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(54) Title: TETRAHYDROBENZOTHIAZOLE ANALOGUES AS NEUROPROTECTIVE AGENTS

(57) Abstract: This invention relates generally to tetrahydrobenzothiazole analogues and tetrahydrobenzooxyzole analogues, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to methods of treatment using these compounds. The invention also encompasses pharmaceutically acceptable esters, amides, and salts of such compounds. The invention further provides a method of reducing or delaying apoptosis in a population of cells, comprising contacting the population of cells with a tetrahydrobenzothiazole analogue or a tetrahydrobenzooxyzole analogue, thereby reducing or delaying apoptosis in the population of cells.

TETRAHYDROBENZOTHIAZOLE ANALOGUES AS NEUROPROTECTIVE AGENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to U. S. Provisional Application Serial No. 60/216,388, filed July 6, 2000, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates generally to tetrahydrobenzothiazole analogues, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to methods of treatment using these compounds.

BACKGROUND OF THE INVENTION

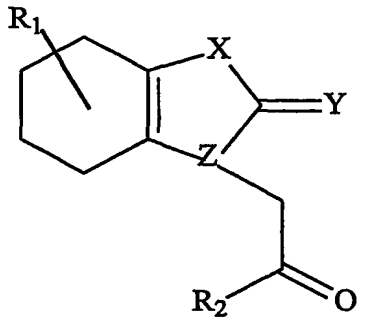
Deposition of neurotoxic forms of amyloid β-peptide (Aβ) in the brain likely contributes to neuronal degeneration and dementia in Alzheimer's Disease (AD) patients. The tumor suppressor protein p53 is a key modulator of stress responses, and activation of p53 precedes apoptosis in many cell types. Morevoer, up-regulation of p53 has been described as a common feature of several neurodegenerative disorders including AD, Parkinson's Disease, stroke, trauma, brain or spinal cord injury, and excitoxic insults. Different triggers, like oxidative damage to DNA, overactivation of glutamate receptors, and disruption of cellular homeostasis, can initiate a cascade of intramolecular events that proceed via p53 activation of a death program called apoptosis. Consequently, the ability to inhibit p53 may be able to protect neurons against apoptotic insults.

In Komarov, P., et al., 285 Science 1733 (1999), pifithrin-α, a p53 inhibitor was studied for its efficiency in reducing the side effects of cancer therapy. This reference did not study novel analogues of tetrahydrobenzothiazoles. Tetrahydrobenzothiazole analogues have been synthesized in the prior art as antihelminthic compounds (anti-

parasitic). One method, which is incorporated by reference in its entirety, is described in Singh, A., et al., 14B Indian J. Chem. 997 (1976), which references Saldabos, I., et al., I Khim. Farm. Zh. 27 (1967), 68 Chem Abstr. 2856 (1968). In this method, tetrahydrobenzothiazole starting materials are treated with α-haloketones in a solvent.

SUMMARY OF THE INVENTION

In accordance with the purpose(s) of this invention, as embodied and broadly described herein, this invention, in one aspect, relates to tetrahydrobenzothiazole analogues comprising one or more analogues of Formula (I):



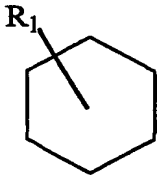
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member

selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

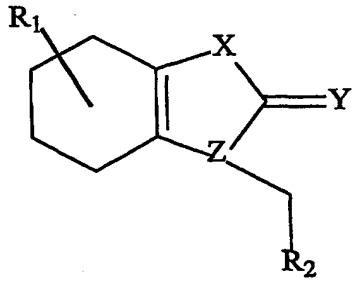
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a second aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (II):



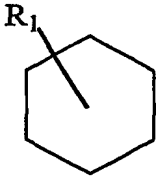
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

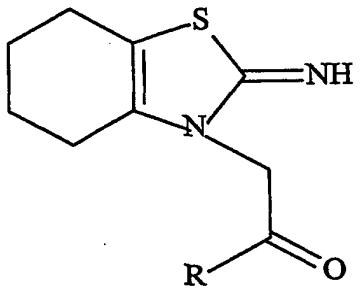
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a third aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

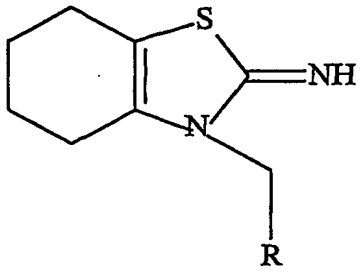
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl;

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a fourth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

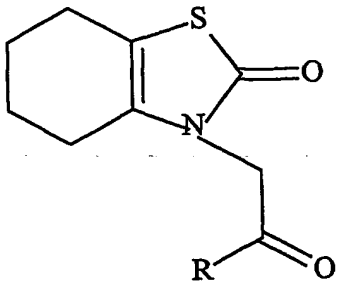
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH,

halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a fifth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

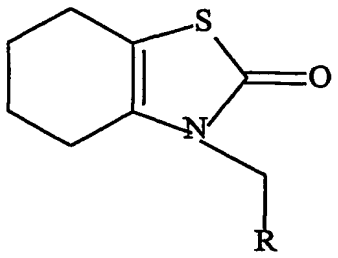
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a sixth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

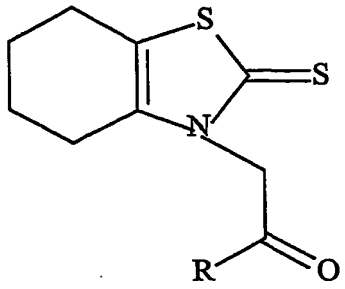
R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a seventh aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

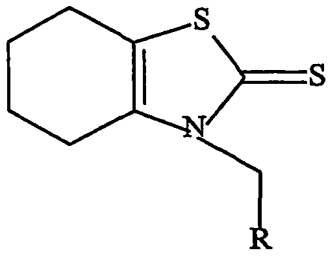
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In an eighth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (VIII):



(VIII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

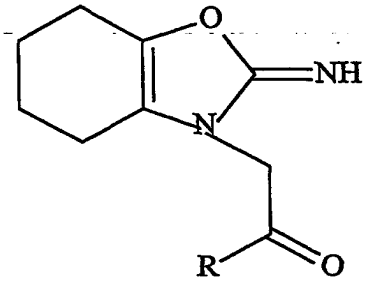
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a ninth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

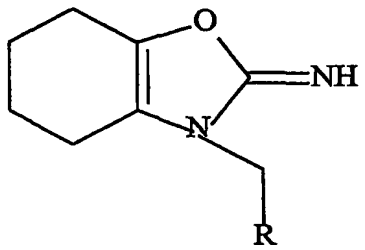
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

In a tenth aspect, the invention relates to tetrahydrobenzothiazole analogues comprising one or more analogues of formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting

of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

The invention also encompasses pharmaceutically acceptable esters, amides, and salts of such compounds, as will be explained in detail, *infra*.

Such compounds of the formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) through (XV) and their pharmaceutically acceptable esters, amides, and salts are referred to herein as the inventive compounds.

In another aspect, the invention relates to pharmaceutical compositions containing the aforementioned inventive compounds in combination with a pharmaceutically acceptable carrier.

The invention further provides a method of reducing or delaying apoptosis in a population of cells, comprising contacting the population of cells with a tetrahydrobenzothiazole analogue, thereby reducing or delaying apoptosis in the population of cells.

In yet another aspect, the invention provides a method of treating a subject with a degenerative condition or of preventing a degenerative condition in a subject,

comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue.

Furthermore, the invention provides a method of treating a subject after an ischemic event to reduce ischemia-induced apoptosis, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue, thereby reducing apoptosis.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides the chemical structures and data for the compounds tested in examples 4 and 5.

Figure 2 shows the effect PFTα (compound 5), its precursor, or analogues thereof on PC12 cells treated with the DNA-damaging agent camptothecin. PC12 cells were pretreated for 6 h with compounds (precursor, 1, 4-11, 13-15) prepared in 0.5% DMSO at concentrations between 100-400 nM) and were then exposed for 24 hours to camptothecin (40 μM). Figure 2A shows the amount of fluorescence emitted by the live-cell indicator dye, 2', 7'-bis(2-carboxyethey)-5-6-carboxyfluorescein AM ester (BCECF AM: 5 μM). This fluorescent dye was taken up and retained by live cells.

Figure 2B shows the quantification of neuronal survival in the cultures (n=3 cultures). PFTα (compound 5) and several of its analogues protected cultured PC12 cells against death induced by camptothecin.

Figure 3 shows the results of a neuronal survival assay using cultured hippocampal neurons treated with either camptothecin or etoposide in the presence and absence of PFTα (compound 5) or its precursor. PFTα protects cultured hippocampal neurons against death induced by DNA-damaging agents camptothecin and etoposide. Hippocampal cell cultures were pretreated for 1 hour with 0.5% DMSO (vehicle), 200 nM PFTα or 200 nM of PFTα precursor. Cultures were then exposed for 24 hours to the DNA-damaging agents camptothecin (5 μM) and etoposide (2.5 μM). Neuronal survival in each culture was quantified (n=4-6 cultures). **$p<0.01$ compared to corresponding value for cultures treated with vehicle or precursor (ANOVA with Scheffe post-hoc tests).

Figure 4 shows the results of a neuronal survival assay using cultured hippocampal neurons treated with either camptothecin or etoposide in the presence and absence of PFTα and its analogues 14, 1, 15, 5x. Compounds were added 1h before exposure of primary hippocampal neurons to the DNA-damaging compounds camptothecin (5μM) or etoposide (2.5μM). The percentage of neuronal survival 24h after the treatment is given for each group as mean ± SD.

Figure 5 shows the results of a neuronal survival assay using cultured hippocampal neurons treated with camptothecin in the presence and absence of PFTα analogues 4, 6-8, 9-11, 13, 16 (100nM). Compounds were added 1h before exposure of primary hippocampal neurons to the DNA-damaging compound camptothecin (5μM). Compounds 8 and 9 significantly protected against toxicity ($p \leq 0.05$).

Figure 6 shows the results of histologic analysis of four different brain levels in mice following transient focal cerebral ischemia with and without pretreatment with PFT-α (compound 5). PFT-α (2mg/kg) was administered intraperitoneally 1h before transient middle cerebral artery occlusion in C57BL/6 mice. Twenty four hours after reperfusion, mice were euthanized and the infarct size was quantified after TTC-staining of 2mm brain sections. Figure 2A shows the infarct area in mm^2 at each level.

Figure 2B shows the infarct volume in mm^3. Values are the mean and SD of 12 animals per group.

Figure 7 shows the results of behavioral tests following PFT-α and compounds 5x and 13 treatment in a MPTP-induced Parkinson's disease model. C57BL/6 mice were given vehicle (control) or MPTP, and PFT-alpha (2mg/kg), compound **5x** (2mg/kg), compound 13 (2mg/kg), or vehicle were administered 30 minutes before the first MPTP injection and again 30 minutes after the last MPTP injection. Mice were tested on a rotarod apparatus. Figure 7A shows the summary data for measurements of numbers of falls. Figure 7B shows the summary data for running times. Values are the mean and SE (standard error) of determinations made in 12 mice/group. (*P<0.01 compared to control value, **P<0.01 compared to MPTP value. ANOVA with Scheffe post-hoc test).

Figure 8 shows the results of densitometric analysis of Western blots stained with a TH antibody. PFT-alpha and compound 5x attenuate MPTP-induced loss of striatal tyrosine hydroxylase. Mice were given saline (control) or MPTP, and PFT-alpha (2mg/kg), compound 5x (2mg/kg), compound 13 (2mg/kg) or vehicle were administered 30 minutes before the first MPTP injection and were repeated 30 minutes after the last MPTP injection. 7 days later, mice were euthanatized and striatal tissue samples were removed. Levels of TH were determined by immunoblot analysis (Western blots). The results of densitometric analysis of blots of samples from 4-6 different mice/group are shown as mean ± SE. (*P<0.01 compared to control value, **P<0.01 compared to MPTP value. ANOVA with Scheffe post-hoc tests).

Figure 9 shows the results of quanitifation of TH-positive cells in the substantia nigra of animals treated with MPTP, with or without PFT-α and compounds 5x and 13. PFT-α and compound 5x attenuated MPTP-induced loss of substantia nigra dopaminergic neurons. Mice were given saline (control) or MPTP, and PFT-alpha (2mg/kg) (compound 5), Z-1-117 (2mg/kg) (compound 5x), Z-1-143 (2mg/kg) (compound 13) or vehicle were administered 30 minutes before the first MPTP injection and were repeated 30 minutes after the last MPTP injection. Values are shown

the mean ± SE of counts made in 4 mice/group. (*P<0.05 , **P<0.01 compared to MPTP value. ANOVA with Scheffe post-hoc tests).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein and to the Figures and their previous and following description.

Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods of using or making as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an aromatic compound" includes mixtures of aromatic compounds, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

References in the specification and concluding claims to parts by weight, of a particular element or component in a composition or article, denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

A weight percent of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $-CO(CH_2)_8CO-$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

The term "halogen" and "halo" refer to bromine, chlorine, fluorine, and iodine.

The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. The term "lower alkyl" intends an alkyl group of from one to six carbon atoms, preferably from one to four carbon atoms. The term "cycloalkane" as used herein refers to a cyclic alkane group.

The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be defined as -OR where R is alkyl as defined above. A "lower alkoxy" group intends an alkoxy group containing from one to six, more preferably from one to four, carbon atoms.

The term "alkylene" as used herein refers to a difunctional saturated branched or unbranched hydrocarbon chain, for example, methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), propylene ($-CH_2-CH_2-CH_2-$), 2-methylpropylene [$-CH_2-CH(CH_3)-CH_2-$], hexylene [$-(CH_2)_6-$] and the like. "Lower alkylene" refers to an alkylene group of from 1 to 6, more preferably from 1 to 4, carbon atoms. The term "cycloalkylene" as used herein refers to a cyclic alkylene group.

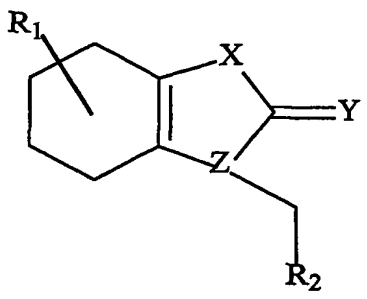
The term "alkene" as used herein intends a mono-unsaturated or di-unsaturated hydrocarbon group. Asymmetric structures such as (AB)C=C(CD) are intended to include both the *E* and *Z* isomers. This may be presumed in structural formulae herein wherein an asymmetric alkene is present, or it may be explicitly indicated by the bond symbol —.

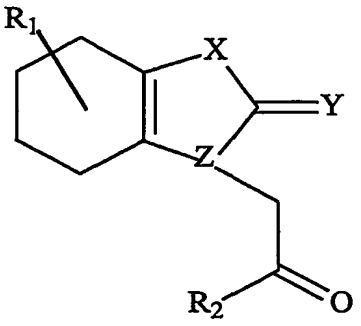
The term "aryl" as used herein refers to a C_6H_6 aromatic ring. Substituents on the aryl group may be present on any position, i.e. *ortho*, *meta* or *para* positions or fused to the aromatic ring.

By "bisphenol" it is meant that two C_6H_6 aromatic rings are present in a group in an unfused state. The aromatic rings may be joined at any position, i.e. *ortho*, *meta* or *para* positions, relative to the attachment position to the structure. Substituents on the bisphenol group may be present on or fused to any position of either aromatic ring.

The term "condensed aromatic" as used herein refers to more than one fused C_6H_6 aromatic ring. The aromatic rings may be fused at any bond i.e. along the C_2-C_3 bond relative to the C_1 attachment position to the structure. Substituents on the condensed aromatic group may be present on or fused to any position of any of the aromatic rings.

By "tetrahydrobenzothiazole" or "tetrahydrobenzothiazole analogue" it is meant to include tetrahydrobenzothiazole analogues, tetrahydrobenzooxyzole analogues, and heterocyclic analogues of the general formulas (GF1) and (GF2):





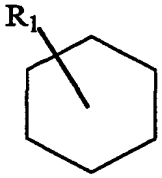
(GF1) (GF2)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH and halogen;

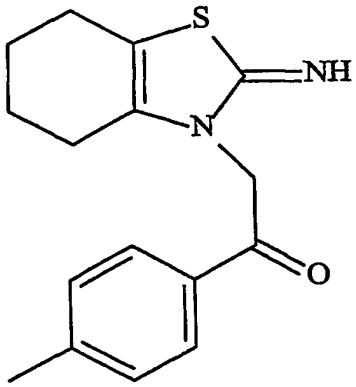
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

By the terms "PFTα," "PFT-a," and "pifithrin-α" is meant [2-(2-imino-4,5,6,7-tetrahydrobenzothiazol-3-yl)-1-p-tolyethanone] which is represented by the chemical structure (PFTα):



(PFTα)

or a pharmaceutically acceptable salt or ester thereof.

By "substituted" is meant that the substituent group may be present anywhere within or attached to the substituted group.

By "neural cell" is meant any cell that can be located in the central or peripheral nervous system or is a precursor or derivative thereof, including, for example, neuronal cells, glial cells, neural stem cells, neuronal stem cells, neuroblasts. By "cardiac cell" is meant any cell that can be located in the cardiac tissue or is a precursor or derivative thereof, including, for example, cardiomyocytes, cardiac stem cells, endothelial cells, and myoblasts. By "pancreatic islet cell" is meant any cells type present in the pancreatic islet or precursors or derivatives thereof, including, for example, alpha cells (glucagon secreting cells) and beta cells (insulin secreting cells). By "muscle cells" is meant skeletal, smooth, or cardiac muscle cells or precursors or derivatives thereof, including, for example, myoblasts. Any of these cell populations can include immortalized cells and can include transfected or transformed cells. Thus, the population of neural cells, cardiac cells, pancreatic cells, or muscle cells can include one or more types of neural cells, cardiac cells, pancreatic cells, or muscle cells.

By "reducing or delaying" is meant either slowing or eliminating all or a portion of the apoptosis so that cell death is diminished or delayed in one or more cells in the cellular population.

As used throughout, by "contacting" is meant an instance of exposure of at least one cell (e.g., a neural cell, a stem cell, a cardiac cell) to an agent (e.g., a tetrahydrobenzothiazole analogue).

As used herein, "a degenerative condition" means a disease or condition marked by cell death. The degenerative condition can include, for example, neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease,

amyotrophic lateral sclerosis, multiple sclerosis, brain and spinal cord injury, peripheral neuropathies, and stroke), degenerative cardiomyopathies (e.g., idiopathic dilated, ischemic, hypertrophic, obstructive, famililal obstructive, familial arrhythmogenic right, ventricular, post-viral, alcoholic, endomyocardial fibrosis, amyloidosis, and muscular dystrophy), degenerative myopathies (e.g., muscular dystrophies), and other degenerative processes (e.g., diabetes Type I or Type II, and ischemia).

As used throughout, by "subject" is meant an individual. Preferably, the subject is a mammal such as a primate, and, more preferably, a human. Thus, the "subject" can include domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.).

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, the phrase "optionally substituted lower alkyl" means that the lower alkyl group may or may not be substituted and that the description includes both unsubstituted lower alkyl and lower alkyl where there is substitution.

In general, "a therapeutically effective dose or doses" means the amount needed to achieve the desired result or results (reducing or delaying apoptosis or treating a degenerative condition). One of ordinary skill in the art will recognize that the potency and, therefore, a "therapeutically effective dose or doses" can vary for the various tetrahydrobenzothiazole analogues used in this invention. One skilled in the art can readily assess the potency of the analogues.

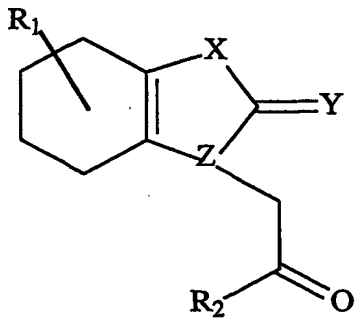
The term "modified" is often used herein to describe polymers and means that a particular monomeric unit that would typically make up the pure polymer has been replaced by another monomeric unit that shares a common polymerization capacity with the replaced monomeric unit. Thus, for example, it is possible to substitute diol residues for glycol in poly(ethylene glycol), in which case the poly(ethylene glycol)

will be "modified" with the diol. If the poly(ethylene glycol) is modified with a mole percentage of the diol, then such a mole percentage is based upon the total number of moles of glycol that would be present in the pure polymer but for the modification. Thus, in a poly(ethylene glycol) that has been modified by 50 mole % with a diol, the diol and glycol residues are present in equimolar amounts.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected bicyclic compound without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

The invention also encompasses pharmaceutically acceptable nontoxic ester, amide, and salt derivatives of those compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), and (X) containing a carboxylic acid moiety.

In one embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of Formula (I):



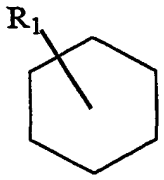
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

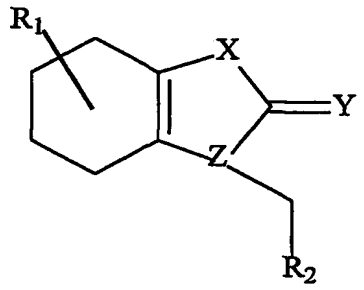
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, preferably one or 3 to 8 carbon atoms, more preferably one, three or four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

In another embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (II):



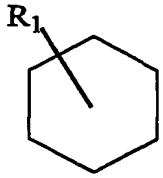
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

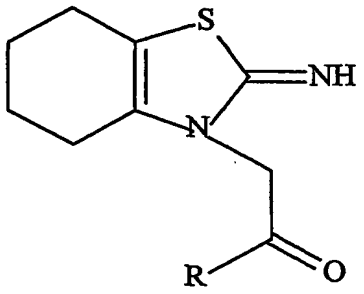
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

In a further embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, preferably one or 3 to 8 carbon atoms, more preferably one, three or four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN,

NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

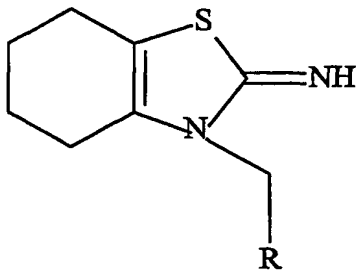
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Some preferred embodiments of formula (III) include where R is ethyl, methoxy, methoxyphenyl, fluorophenyl, chlorophenyl, nitrophenyl, or tetradecyloxyphenyl.

Moreover, in another embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from

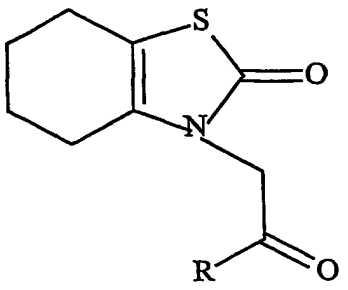
the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (IV) include where R is ethyl, methoxy, methoxyphenyl, fluorophenyl, chlorophenyl, nitrophenyl, or tetradecyloxyphenyl.

In still a further embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

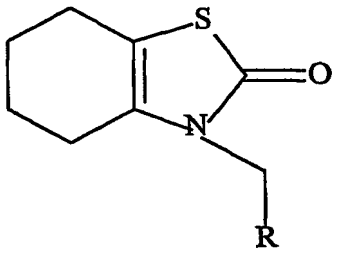
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more

preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (V) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

In another preferred embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted

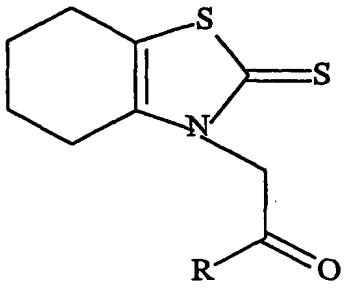
with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (VI) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

In another preferred embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more

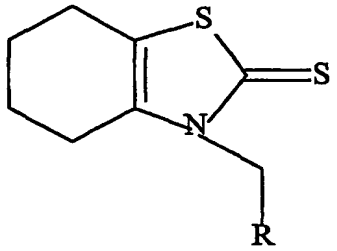
preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (VII) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

A preferred embodiment of the present invention includes the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VIII):

(VIII)



or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

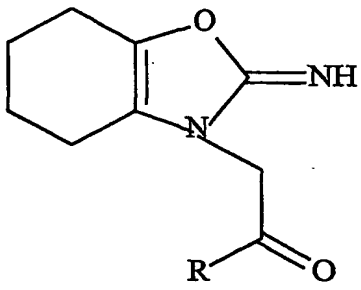
(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (VIII) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

In another preferred embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted

with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

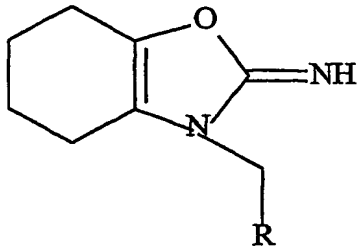
(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (IX) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

In another preferred embodiment, the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably from 1 to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, preferably one to 8 carbon atoms, more preferably one to four carbon atoms, wherein the carbon chain is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy; preferably substituted with at least one member selected from

the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; preferably substituted with at least one member selected from the group consisting of OH, COOH, halogen, and C_1-C_8 alkyl; more preferably substituted with at least one member selected from the group consisting of OH, COOH, Cl, F, Br, and C_1-C_4 alkyl.

Preferred embodiments of formula (X) include where R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

In a preferred embodiment for each of the tetrahydrobenzothiazole analogues having the formula (I), (II), (III), (IV), (V), (VII), (VIII), (IX), or (X), subparts (b), (c), (d), and (e) or formula (VI), subparts (a), (b) and (c) may preferably be C_1-C_8 alkenyl or C_1-C_8 alkynyl, more preferably C_1-C_4 alkenyl or C_1-C_4 alkynyl.

In one embodiment of the method of reducing or delaying apoptosis, the tetrahydrobenzothiazole analogue is pififthrin-α. Alternatively, the tetrahydrobenzothiazole analogue is selected from the group of analogues having formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) or (XI) through (XV).

The present method is useful in reducing or delaying apoptosis induced by a toxin (e.g., the neurotoxic form of amyloid β-peptide, camptothecin, glutamate, anti-cancer drugs, such as etoposide and derivatives thereof; vinca alkaloids; and chemical agents, such as 3-nitropropionic acid, 1-methyl-4-phenyl-1, 2, 3,l 6-tetrahydropyridine (MPTP), domoic acid, and kainic acid), ischemia (e.g., caused by a stroke, transient ischemic attack, myocardial infarction), trauma (e.g., head injury), genetic defect (e.g., mutations in amyloid precursor protein; presenilins; α-synuclein; copper, zinc superoxide dismutase; Notch3 gene), genetic disease (e.g., muscular dystrophy, Huntington's disease, CADISIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), environmental factors, (e.g., irradiation or severe seizure disorders).

Also provided is a method of treating a subject with a degenerative condition or of reducing one or more symptoms of a degenerative condition in a subject, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue. The degenerative condition may result from events such as, but not limited to, surgery or organ transplant, trauma, severe seizure disorder, environmental factors, toxins, ischemia, genetic defects or diseases. With such conditions, one embodiment of the present invention provides a method of treating a subject before a surgical procedure to reduce apoptosis, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue, thereby reducing apoptosis. In another embodiment, the invention provides a method of treating a subject after an excitoxic event. Such methods are also useful in treating a subject before a trigger event such as an ischemic or excitoxic event when such an event can be foreseen. In another embodiment, the invention provides a method of treating a subject after an ischemic event to reduce ischemia-induced apoptosis, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue, thereby reducing apoptosis.

The invention also provides a method of treating a subject exposed to irradiation, comprising administering to the subject a therapeutically effective amount

of a tetrahydrobenzothiazole analogue, thereby reducing one or more of the undesired symptoms of irradiation. In one embodiment, the irradiation is caused by radiation therapy. The irradiating event, in another embodiment, results in radiation poisoning. Thus, the analogue is administered before, during, or after the irradiating event.

Pharmaceutically acceptable salts are prepared by treating the free acid with an appropriate amount of a pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are ammonium hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, aluminum hydroxide, ferric hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, and the like. The reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from about 0°C to about 100°C, preferably at room temperature. The molar ratio of compounds of structural formula (I) to base used are chosen to provide the ratio desired for any particular salts. For preparing, for example, the ammonium salts of the free acid starting material–a particular preferred embodiment–the starting material can be treated with approximately one equivalent of pharmaceutically acceptable base to yield a neutral salt. When calcium salts are prepared, approximately one-half a molar equivalent of base is used to yield a neutral salt, while for aluminum salts, approximately one-third a molar equivalent of base will be used.

Ester derivatives are typically prepared as precursors to the acid form of the compounds, as illustrated in the examples below, and accordingly may serve as prodrugs. Generally, these derivatives will be lower alkyl esters such as methyl, ethyl, and the like. Amide derivatives -(CO)NH_2, -(CO)NHR and -(CO)NR_2, where R is lower alkyl, may be prepared by reaction of the carboxylic acid-containing compound with ammonia or a substituted amine.

Synthetic Methods:

The compounds of the invention may be readily synthesized using techniques generally known to synthetic organic chemists. Suitable experimental methods for making and derivatizing aromatic compounds are described, for example, in the references cited in the Background section herein above, the disclosures of which are hereby incorporated by reference for their general teachings and for their synthesis teachings. Methods for making specific and preferred compounds of the present invention are described in detail in the Examples.

Utility and Administration:

The compounds of the invention defined by structural formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) through (XV), including the pharmacologically acceptable esters, amides or salts thereof, are useful in reducing or delaying apoptosis in a population of cells, comprising contacting the population of cells with a tetrahydrobenzothiazole analogue, thereby reducing or delaying apoptosis in the population of cells. In one embodiment, the cells are neural cells, and in another embodiment, the cells are cardiac cells. In another embodiment, the cells are pancreatic islet cells, and in yet another embodiment, the cells are muscle cells.

Preferably, the reduction or delay in apoptosis would be at least a 10% reduction or delay, including, for example, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or any amount in between. The reduction or delay can be measured, for example, by comparing the number of cells after contact with the tetrahydrobenzothiazole analogue to the number of cells in a control population of cells lacking contact with the tetrahydrobenzothiazole analogue. Histological signs of apoptosis that would be reduced or delayed in cells after contact with the tetrahydrobenzothiazole analogue include condensation of the chromatin, the occurrence of apoptotic bodies, and cellular shrinkage. DNA laddering and other signs of DNA degradation are also signs of apoptosis which would be reduced or delayed after contact with the tetrahydrobenzothiazole analogue. Apoptosis can also be assessed indirectly by observing, for example, a reduction in the amount of release or

activity by the population of cells. Thus, if the cell population undergoes apoptosis, neurotransmitter release upon stimulation of neuronal cells would decrease. Similarly, a decrease in cardiac muscle contraction or cardiac output is an indicator of apoptosis. It is understood that one or a combination of indicators of apoptosis may show a delay or reduction.

The cell can be contacted *in vitro* with the agent, for example, by adding the agent to the culture medium (by continuous infusion, by bolus delivery, or by changing the medium to a medium that contains the agent) or by adding the agent to the extracellular fluid *in vivo* (by local delivery, systemic delivery, intravenous injection, bolus delivery, or continuous infusion). *In vitro* contact may be preferred, for example, in reducing or delaying apoptosis in a population of cells to be transplanted into a donor. *In vivo* contact may be preferred in reducing or delaying apoptosis in a subject with a disease, condition, or injury associated with apoptosis. The duration of "contact" with a cell or population of cells is determined by the time the agent is present at physiologically effective levels or at presumed physiologically effective levels in the medium or extracellular fluid bathing the cell or cells. Preferably, the duration of contact is 1-96 hours and, more preferably, for 24 hours, but such time would vary based on the half life of the agent and could be optimized by one skilled in the art using routine experimentation.

It is understood that the tetrahydrobenzothiazole analogue is administered in a therapeutically effective dose or doses to reduce or delay apoptosis. The agents used in this invention (i.e., tetrahydrobenzothiazole analogues) can be administered *in vitro* in an amount of about 10 nmol to 100μmol. More preferably the agent is administered *in vitro* in an amount of about 1.0 nmol to 10μmol. Necessary modifications in this dosage range may be determined by one of ordinary skill in the art.

The agents used in this invention are administered *in vivo* to a subject in need thereof by commonly employed methods for administering agents in such a way to bring the agent in contact with the population of cells. The agents of the present

invention can be administered orally, parenterally, transdermally, extracorporeally, topically or the like, although intravenous administration is typically preferred.

The agents of the present invention can also be administered using gene therapy methods of delivery. See, e.g., U.S. Patent No. 5,399,346, which is incorporated by reference herein. Using a gene therapy method of delivery, primary cells transfected with the gene for the agent of the present invention can additionally be transfected with tissue specific promoters to target specific organs, tissue, grafts, or cells.

The dosage of the agent varies depending on the type of disease or condition, degree of apoptosis, weight, age, sex, and method of administration. Also, the dosage of the agent varies depending on the target cell, tissue, graft, or organ. Generally, the agents can be orally or intravenously administered *in vivo* in an amount of about 0.01-1000 mg/kg. More preferably, the agent is administered *in vivo* in an amount of about 0.1 to 100 mg/kg. Even more preferably, the agent is administered in an amount of about 5mg/kg. Thus, an administration regimen could include long-term, daily treatment. By "long-term" is meant at least two weeks and, preferably, several weeks, months, or years of duration. Necessary modifications in this dosage range may be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein. See *Remington's Pharmaceutical Sciences* (Martin, E.W., ed., latest edition), Mack Publishing Co., Easton, PA. The dosage can also be adjusted by the individual physician in the event of any complication.

The agents can be administered conventionally as compositions containing the active agent as a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent, i.e., carrier or vehicle. Depending on the intended mode of administration, the agent can be in pharmaceutical compositions in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) (XI) through (XV) include, as noted above,

an effective amount of the selected compound in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Thus, the compositions are administered in a manner compatible with the dosage formulation and in a therapeutically effective amount. As discussed above, precise amounts of active ingredient required to be administered depend on the judgment of the practitioner and are peculiar to each individual.

For oral administration, fine powders or granules may contain diluting, dispersing, and/or surface active agents, and may be presented in water or in a syrup, in capsules or sachets in the dry state, or in a nonaqueous solution or suspension wherein suspending agents may be included, in tablets wherein binders and lubricants may be included, or in a suspension in water or a syrup. Where desirable or necessary, flavoring, preserving, suspending, thickening, or emulsifying agents may be included. Tablets and granules are preferred oral administration forms, and these may be coated.

Parenteral administration, if used, is generally characterized by intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous, intra-articular and intratracheal routes of injection. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a

constant dosage is maintained. See, e.g., U.S. Patent No. 3,610,795, which is incorporated by reference herein. The agents can also be administered using polymer based delivery systems, including, for example, microencapsulation as described in Langer (1998). Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

For topical administration, liquids, suspension, lotions, creams, gels or the like may be used as long as the active compound can be delivered to the surface of the skin.

Experimental

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices, and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

The dotted lines attached to the benzene ring of structures 4-25 in the examples denote a chemical bond and not an additional carbon atom. Thus the R group of structure 4 is chemically bonded to Formula (XI) at the *para* position relative to the Fluorine atom. Throughout these examples, the dotted lines are meant to be a bond attachment and not an additional carbon atom.

Numbers in bold and parenthesis correspond to structures depicted in the examples for formula (XI) of example 1 and formula (XII) of example 2.

Synthesis of the intermediate 2-amino-4,5,6,7-tetrahydrobenzothiazole

A mixture of cyclohexanone (1.96 g, 0.02 mmol), thiourea (3.04 g, 0.04 mmol) and iodine (5.08 g, 0.02 mmol) was stirred in a 110°C oil bath for 12 h. The reaction mixture then was cooled, dissolved in boiling water and extracted with ether to remove any ketone and iodine. The solution was made basic with solid $NaHCO_3$, yellow crystals thereafter precipitated and were collected by filter to give 2-amino-4,5,6,7-tetrahydrobenzothiazole hydrogen iodide (3.2 g, 57%), m.p. 185-187°C. ^1H NMR (DMSO-d_6): 2.50-2.48 (m, 4 H), 1.78-1.75 (m, 4 H). ^{13}C NMR (DMSO-d_6): 168.6, 140.7, 116.3, 26.1, 24.1, 24.0, 23.6. 2-amino-4,5,6,7-tetrahydrobenzothiazole hydrogen iodide (0.5 g) then was dissolved in hot saturated aqueous Na_2CO_3, and on cooling 2-amino-4,5,6,7-tetrahydrobenzothiazole was gained as white needle crystals (0.25g, 93%), m.p. 87-88°C.

Example 1

Synthesis of Z-1-110: 1-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-2-butanone hydrobromide (1)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (76 mg, 0.49 mmol) and 1-bromo-2-butanone (51 µl, 0.50 mmol) in benzene (10 ml) was stirred at room temperature for two days. The resulting precipitate was filtered off from the reaction mixture and washed with a small amount of ethanol and benzene to give 1-(4,5,6,7-tertahydro-benzothiazolyl)-2-butanone hydrobromide (1) (75 mg, 50%) as pale yellow crystals. mp 114-115°C ^1H NMR (DMSO-d_6): δ 9.45 (s, 1 H), 5.06 (s, 2 H), 2.64 (q, J = 7.2 Hz, 2 H), 2.41-2.52 (m, 2 H), 2.29 (br, 2H), 1.73 (br, 4H), 0.99 (t, J = 7.2 Hz, 3 H); Anal. Calcd. HR-MS m/z calcd for $C_{11}H_{17}N_2OS$ 225.1062, found 25.1071. Anal. Calcd. $C_{11}H_{17}BrN_2OS$: C, 43.18; H, 5.61. Found: C, 43.23; H, 5.56.

Synthesis of PFT-α (Z-1-073): 1-(4-methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (5)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (2) (154 mg, 1 mmol) and 2-bromo-4'-methylacetophone (213 mg, 1 mmol) in dry benzene (20 ml) was stirred at room temperature for two days. Thereafter, the precipitate was filtered off from the reaction mixture and washed with a small amount of benzene to afford 1-(4-methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (5) (247 mg, 67%) as white crystals. mp 180°C (EtOH/EtOAc) (lit[20]: 182°C); ^{1}H NMR (DMSO-d_6): δ 8.85 (s, 1 H), 7.96 (d, J = 8.1 Hz, 2 H), 7.45 (d, J = 8.1 Hz, 2 H), 5.70 (s, 2 H), 2.55-2.30 (m, 7 H), 1.73 (m, 4 H).

The following compounds were synthesized in accordance with the methods above, except the products were crystallized from MeOH/EtOAc, Z-1-189: ethyl 2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrobromide (2),: yield (52%); mp 224°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.63 (s, 1H), 4.93 (s, 2H), 4.21 (q, J = 7.1Hz, 2H), 2.38 (m, 2H), 1.73 (m, 4H), 1.24 (t, J = 7.1Hz, 3H),

ethyl 2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrohalide (2a),

methyl 2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrohalide (3),

Z-1-135: 1-(4-fluorophenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (4): 44%, ^{1}H NMR (DMSO-d_6): 9.51 (s, 1 H), 8.14 (d, J = 5.5 Hz and J = 8.7 Hz, 2 H), 7.49 (t, J = 8.7 Hz, 2 H), 5.74 (s, 2 H), 2.55-2.34 (m, 4 H), 1.73 (m, 4 H). HR-MS m/z calcd for $C_{15}H_{16}FN_2OS$ 291.0967, found 291.0964. Anal. ($C_{15}H_{16}BrFN_2OS$) C, H, N,

1-(4-fluorophenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (4a),

Z-1-117: 1-(4-methylphenyl)-2-(4,5,6,7-tertahydro-2-imino-6-methyl-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (5x): 54%; mp 254-256°C (lit[20] 278°C); ^{1}H NMR (DMSO-d_6): 9.60 (s, 1 H), 7.95 (d, J = 8.2 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 5.70 (s, 2 H), 2.71-2.64 (m, 1 H), 2.51-2.31 (m, 5 H), 2.21-2.12 (m, 1 H), 1.83-1.79 (m, 2 H), 1.36 (br, 1 H), 1.02 (d, J = 6.5 Hz, 3 H). Anal. ($C_{17}H_{21}BrN_2OS$) C, H, N,

1-(4-methylphenyl)- 2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrohalide (5xx),

Z-1-133: 1-(4-methoxylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (6): 61%; ^{1}H NMR (DMSO-d_6): 9.47 (s, 1 H), 8.03 (d, J = 8.9 Hz, 2 H), 7.16 (d, J = 8.9 Hz, 2 H), 5.67 (s, 2 H), 3.89 (s, 3 H), 2.55 (br, 2 H), 2.32 (br, 2 H), 1.73 (br, 4 H). HR-MS m/z calcd for $C_{16}H_{19}N_2O_2S$ 303.1167, found 303.1158. Anal. ($C_{16}H_{19}BrN_2O_2S$) C, H, N,

1-(4-methoxyphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (6a),

Z-1-138: 1-(2-methoxylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (7): 17%, ^{1}H NMR (DMSO-d_6): 7.70-7.12 (m, 4 H), 5.42 (s, 2 H), 3.99 (s, 3 H), 2.50-2.39 (m, 4 H), 1.81 (br, 4 H). HR-MS m/z calcd for $C_{16}H_{19}N_2O_2S$ 303.1167, found 303.1173. Anal. ($C_{16}H_{19}BrN_2O_2S$) C, H, N,

1-(2-methoxyphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (7a),

Z-1-139: 1-(3-methoxylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (8): 52%, mp 143-145°C; ^{1}H NMR (DMSO-d_6): 9.50 (s, 1 H), 7.67-7.37 (m, 4 H), 5.74 (s, 2 H), 3.86 (s, 3 H), 2.55-2.33 (m, 4H), 1.73 (br, 4 H). HR-MS m/z calcd for $C_{16}H_{19}N_2O_2S$ 303.1167, found 303.1171. Anal. ($C_{16}H_{19}BrN_2O_2S$) C, H, N,

1-(3-methoxyphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (8a),

Z-1-141: 1-(4-chlorophenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (9): 70%; ^{1}H NMR (DMSO-d_6): 9.52 (s, 1 H), 3.06 (d, J = 8.6 Hz, 2 H), 7.73 (d, J = 8.6 Hz, 2 H), 5.74 (s, 2 H), 2.55-2.33 (m, 4 H), 1.72 (br, 4 H),

1-(4-chlorophenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrohalide (9a),

Z-1-145: 1-(4-phenylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (10) : 58%; ^{1}H NMR (DMSO-d_6): 9.55 (s, 1 H), 8.15(d, J = 8.5 Hz, 2 H), 7.81 (d, J = 7.0 Hz, 2 H), 7.57-7.44 (m, 4 H), 5.80 (s, 2 H), 2.56-2.36 (m, 4 H), 1.74 (br, 4 H),

1-(4-phenylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrohalide (10a),

Z-1-153: 1-(4-nitrophenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (11): 61%, ^{1}H NMR (DMSO-d_6): 9.54 (s, 1 H), 8.46 (d, J = 8.9 Hz, 2 H), 8.28 (d, J = 8.9 Hz, 2 H), 5.80 (s, 2 H), 2.56-2.37 (m, 4 H), 1.74 (br, 4 H). HR-MS m/z calcd for $C_{15}H_{16}N_3O_3S$ 318.0912, found 318.0903. Anal. ($C_{15}H_{16}BrN_3O_3S$) C, H, N,

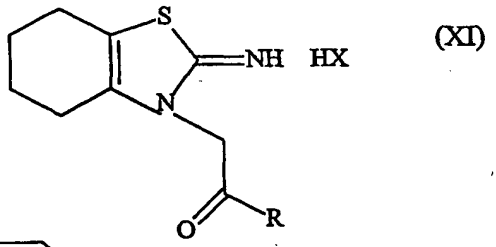
1-(4-nitrophenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (11a),

1-(4-tetradecyloxyphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (12),

Z-1-143: 1-phenyl-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide (13): 58%, mp 151-152°C; ^{1}H NMR (DMSO-d_6): 9.53 (s, 1 H), 8.07-

8.04 (m, 2 H), 7.79-7.74 (m, 1 H), 7.66-7.62 (m, 2 H), 5.75 (s, 2 H), 2.55-2.33 (m, 4H), 1.72 (br, 4 H). HR-MS m/z calcd for $C_{15}H_{17}N_2OS$ 273.1162, found 273.1058. Anal. ($C_{15}H_{17}BrN_2OS$) C, H, N,

1-phenyl-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrohalide (13a), and



(XI)

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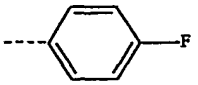
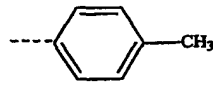
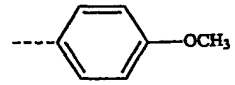
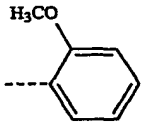
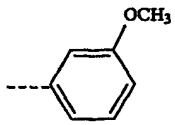
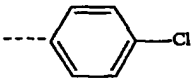
2. R= O 
3. R=O
4. R= 

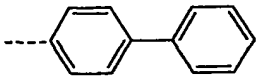
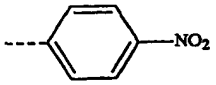
5. R= 

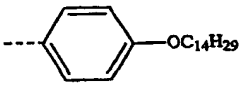
6. R= 

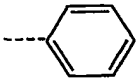
7. R= 

8. R= 

9. R= 

10. R= 
11. R= 

12. R= 

13. R= 

Example 2

Synthesis of Z-1-119: 3-(phenylmethyl)-4,5,6,7-tetrahydro-2(3*H*)-benzothiazolimine hydrobromide (14)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (101 mg, 0.66 mmol) and benzyl bromide (115 mg, 0.67 mmol) in THF (5 mL) was refluxed for two days. The precipitate was collected by filter, washed with a small amount of THF, and recrystallized from ethanol-ethyl ether to afford compound (14) (75 mg, 75%) as pale yellow crystals; mp 271°C; ^{1}H NMR (DMSO-d_6): 9.63 (s, 1 H), 7.45-7.35 (m, 3 H), 7.15 (d, J = 7.1 Hz, 2 H), 5.29 (s, 2 H), 2.50-2.30 (m, 4 H), 1.76 (br, 4 H); HR-MS m/z calcd for $C_{14}H_{17}N_2S$ 245.1112, found 245.1104. Anal. ($C_{14}H_{17}BrN_2S$) C, H, N.

2-imino-3-benzyl-4,5,6,7-tetrahydro-3(2H)- benzothiazole hydrohalide (14a).

Synthesis of Z-1-113: 3-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2(3*H*)-benzothiazolimine hydrobromide (15)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (52 mg, 0.34 mmol) and (bromomethyl)cyclopropane (47 mg, 97%, 0.34 mmol) in ethanol (5 mL) was refluxed for one day. Thereafter, the solvent was evaporated under vacuum. The residue was extracted with hot benzene, filtered and washed with benzene to gain a pale yellow solid that then was recrystallized from ethanol-ethyl ether to afford (15) (60 mg, 61%) as pale yellow crystals; mp 239-240°C; ^{1}H NMR (DMSO-d_6): 3.88 (d, J = 7.0 Hz, 2 H), 2.52-2.39 (m, 4 H), 1.76-1.71 (m, 4 H), 1.09 (br, 1 H), 0.55-0.53 (m, 2 H), 0.42-0.40 (m, 2 H); HR-MS m/z calcd for $C_{11}H_{17}N_2S$ 209.1112, found 209.1115. Anal. ($C_{11}H_{17}BrN_2S$) C, H, N.

2-imino-3-cyclopropylmethyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (15a),

The following compounds were synthesized in accordance with the methods for the synthesis of compounds (19) Z-1-165.

Z-1-165: 2-imino-3-(4'-*tert*-butylbenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (19)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (101 mg, 0.66 mmol) and 4-(tert-butyl) benzyl bromide (154 mg , 0.66 mmol) in THF (5 ml) was refluxed for two days. The resulting precipitate was collected by filter and washed with a small amount of THF and EtOH, and recrystallized from MeOH/EtOAc to give 2-imino-3-(4-*tert*-butylbenzyl)-4,5,6,7-tetrahydro-3(2H)-benzothiazole hydrobromide (98 mg, 39%) as white crystals.

mp 255-257°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.55 (s, 1H), 7.43 (d, J = 8.4Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 5.22 (s, 2H), 2.38 (m, 2H), 1.72 (m, 4H), 1.26 (s, 9H); Anal. ($C_{18}H_{25}BrN_2S \cdot 0.25H_2O$) C, H, N,

Z-1-167: 2-imino-3-phenylethyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole (25),

The mixture of 2-amino-4,5,6,7-tetrahydrobenzothiazole (110 mg), 2-bromoethylbenzene (135 mg), KI (110 mg) in ethanol (5 mL) was refluxed for one day. The solvent was evaporated under vacuum. The residue was neutralized with saturated aqueous Na_2CO_3 solution. The product was separated from the aqueous solution as an uncrystallizable oil, and recrystallized from MeOH/EtOAc to give compound as pale brown crystal (yield 38%); mp 262°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.33 (br, 1H), 7.32-7.20 (m, 5H), 4.06 (t, J = 6.9 Hz, 2H), 2.92 (t, J = 6.9 Hz, 2H), 2.42 (m, 2H), 2.14 (m, 2H), 1.61 (m, 4H),

2-imino-3-phenylethyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (25a),

Z-1-181 2-imino-3-(4′-fluorobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (16), yield (41%); mp 252°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.61 (s, 1H), 7.30-7.23 (m, 4H), 5.26 (s, 2H), 2.36 (m, 2 H), 1.71 (m, 4 H),

2-imino-3-(4-fluorobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (16a),

Z-1-163: 2-imino-3-(2′,4′-difluorobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (17),: yield (45%) ; mp 263-264°C (MeOH/EtOAc); ^{1}H NMR (DMSO-

d_6) δ 9.66 (s, 1H), 7.42-7.36 (m, 1H), 7.15-7.11 (m, 2 H), 5.28 (s, 2H), 2.33 (m, 2H), 1.70 (m, 4H),

2-imino-3-(2,4-difluorobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (17a),

Z-1-179: 2-imino-3-(4'-methylbenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (18), : yield (39%) ; mp 253°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.58 (s, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 5.22 (s, 2H), 2.35 (m, 2H), 2.29 (s, 3H), 1.70 (m, 4H),

2-imino-3-(4-methylbenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (18a),

Z-1-161: 2-imino-3-(4'-nitrobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (20),: yield (44%); mp 235-236°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.75 (s, 1H), 8.37 (d, J = 8.8Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 5.52 (s, 2H), 2.59 (m, 2H), 2.41 (m, 2H), 1.80 (m, 4H),

2-imino-3-(4-nitrobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (20a),

Z-1-183: 2-imino-3-(4'-cyanobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (21), : yield (32%); mp 247°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.64 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 5.38 (s, 2H), 2.33 (m, 2H), 1.73 (m, 4H),

2-imino-3-(4-cynobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (21a),

Z-1-175: 2-imino-3-(4'-trifluorobenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (22), : yield (40%); mp 265-266°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.68 (s, 1H), 7.80 (d, J = 8.0Hz, 2H), 7.38 (d, J = 8.0Hz, 2H), 5.41 (s, 2H), 2.55 (m, 2H), 2.35 (m, 2H), 1.72 (m, 4H); Anal. ($C_{15}H_{16}BrF_3N_2S \cdot H_2O$) C, H, N,

2-imino-3-(4-trifluoromethylbenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (22a),

2-imino-3-(4-phenylbenzyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (23),

Z-1-171: 2-imino-3-(naphthalenylmethyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (24), : yield (34%); mp 268°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.66 (s, 1H), 8.0-7.92 (m, 3H), 7.64 (s, 1H), 7.56-7.53 (m, 2H), 7.33 (d, J = 7.2 Hz, 1H), 5.44 (s, 1H), 2.54 (m, 2H), 2.39 (m, 2H), 1.68 (m, 4H).

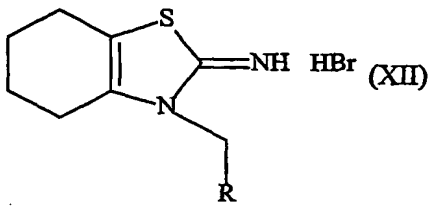
2-imino-3-(2-menaphthyl)-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (24a),

Z-1-187: 2-Imino-3-butyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrobromide (26), yield (19%); ^{1}H NMR (DMSO-d_6) δ 9.34 (s, 1H), 3.87 (t, J = 7.1 Hz, 2H), 1.77 (m, 4H), 1.57 (m, 2H), 1.34 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H),

2-imino-3-butyl-4,5,6,7-tetrahydro-3(2*H*)-benzothiazole hydrohalide (26a),

Z-2-007: 1-(4-methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzoxazolyl)-ethanone hydrobromide (27): yield (51%); mp 237°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.64 (br, 1H), 7.95 (d, J = 8.0Hz, 2H), 7.46 (d, J = 8.9Hz, 2H), 5.78 (s, 2H), 2.52 (br, 2H), 2.44 (s, 3H), 2.33 (m, 2H), 1.77 (m, 4H

Z-2-013: 1-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzoxazolyl)-2-butanone hydrobromide (28): yield (57%); mp 206°C (MeOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.56 (s, 1H), 4.95 (s, 2H), 2.59 (q, J = 7.2Hz, 2H), 2.27 (m, 2H), 1.78-1.69 (m, 4H), 0.99 (t, J = 7.2 Hz, 3H),



(XII)

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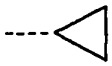
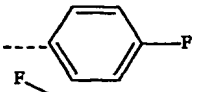
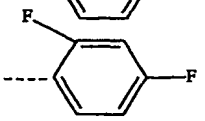
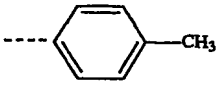
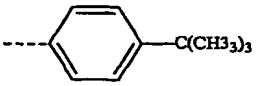
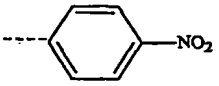
15. R= 

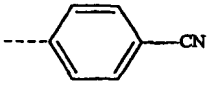
16. R= 

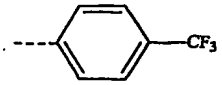
17. R= 

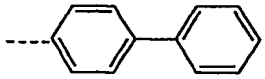
18. R= 

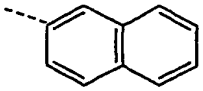
19. R= 

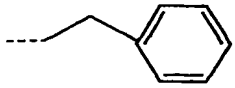
20. R= 

21. R= 

22. R= 

23. R= 

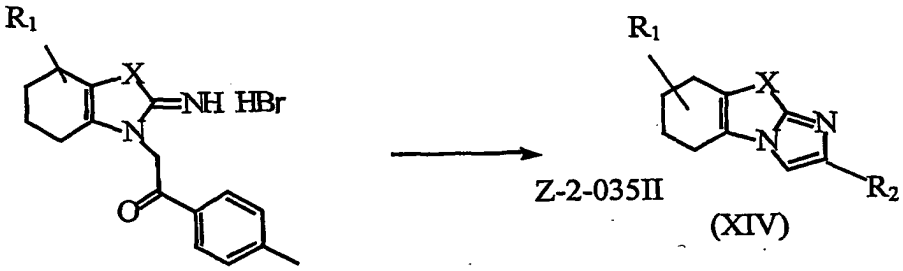
24. R= 

25. R= 

26. R= 

5

Scheme A



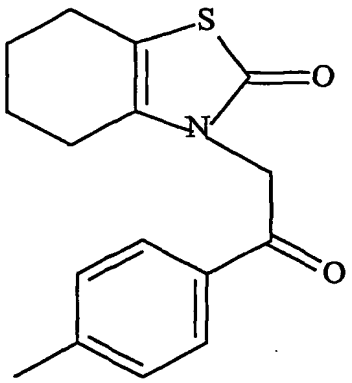
Z-2-035II: 2-(4'-methylphenyl)-5,6,7,8-tetrahydroimidazo[2,1-b]benzothiazole (29), mp 187°C (MeOH/EtOAc) (lit 185°C); ^{1}H NMR (DMSO-d_6) δ 7.71 (d, J = 8.1Hz, 2H), 7.50 (s, 1H), 7.19 (d, J = 8.1Hz, 2H), 2.70-2.63 (m, 4H), 2.35 (s, 3H), 1.95-1.93 (m, 4H).

Compound	R_1	X
29	H	S
	CH_3	O

wherein R_2 is C_{1-8} alkyl or aryl substituted or unsubstituted

Example 3

A mixture of 2, 3, 4, 5, 6, 7-hexahydrobenzothiazolin-2-one (0.1 mol) and sodium hydride (0.1 mol) in toluene (20 ml) was refluxed for half an hour. 2-bromo-4'-methylacetophenone (0.1 mol) was added and the reaction mixture was refluxed for an additional four hours. The precipitated sodium bromide was filtered off and the toluene was removed under vacuum. The crude product was purified to give 3-*p*-methylphenacyl-2, 3, 4, 5, 6, 7-hexahydrobenzothiazolin-2-one (XIII) in the yield of 48%. HNMR ($CDCl_3$): 7.88 (d, J=8.0 Hz, 2 H), 7.28 (d, J=8.0 Hz, 2 H), 5.04 (s, 2 H), 2.42 (br, 5 H), 2.19-2.17 (m, 2 H), 1.82-1.78 (m, 4 H).



(XIII)

Example 4

Neuroprotective Activity of PFTα, its Precursor, and Analogues in PC12 cells

The 2-amino-4,5,6,7-tetrahydrobenzothiazole hydrogen iodide, 1-(4-methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide, and analogues were tested for their ability to protect PC12 cells against the toxic agent, camptothecin. See Figures 2a and 2b. PC12 cells were cultured in RPMI1640 media containing 10% horse serum and 5% fetal calf serum (37°C, pH 7.4) until confluent. Thereafter, 2.2 x 10^4 cells per mL were added to each trough of a 96 well plate (approximately 6,270 cells per well 285 μL) and were left to grow for 12 h. The media then was removed and was replaced by media with and without the compounds to be tested, including precursor, PFTα, and numerous analogues (concentration 100-400 nM, prepared in DMSO to a final dilution of 0.4%, 8 wells per concentration). Following 6 h of incubation, camptothecin (40 μM) was added to 4 of each 8 wells, and the cells were incubated for a further 24 h. Cells then were gently washed twice with phosphate buffered saline (PBS: 0.1 M, 37°C, pH 7.4) and were incubated in PBS containing the live-cell indicator dye, 2', 7'-bis(2-carboxyethey)-5-6-carboxyfluorescein AM ester (BCECF AM: 5 μM) (Molecular Probes, CA), for 45 min in minimal light. This fluorescent dye was taken up and retained by live cells. Finally,

the cells were washed twice in PBS and their fluorescence then was quantified (excitation: 490nm, emission: 535nm, Perkin Elmer HTS 7000). See Figure 2A.

PC12 cell survival was also assessed. The results are shown in Figure 2B. One hundred percent cell survival was determined from cells incubated in the absence of both any compound and camptothecin. One hundred percent cellular death was determined from cells incubated in the absence of any compound and presence of camptothecin, which in prior studies was found to occur at a minimum concentration of 40 μM. Compound-induced toxicity was assessed by comparing cells treated with compound at various concentrations in the absence of camptothecin with cells incubated in the absence of both compound and camptothecin. In the presence of PFTα, neuronal survival of PC12 cells was increased up to 70% as compared to the PC12 cells treated with the DNA damaging agent, camptothecin, in the absence of PFTα. The precursor, 2-amino-4,5,6,7-tetrahydrobenzothiazole hydrogen iodide, showed low activity under the same conditions. No compound was found to induce PC12 cell toxicity at the maximal concentration assessed (400 nM). Compound-induced cellular protection was assessed by comparing cells incubated with camptothecin with cells incubated with camptothecin in the presence of compound, in a concentration-dependent manner. Finally, the natural fluorescence of each compound was quantified in the absence of cells and BCECF AM, and was found to be negligible. A 50% protective concentration (PC_{50}), commensurate with an IC_{50} (concentration required to inhibit 50% of p53 activity), was calculated by transforming the data into a logit format (logit = ln(% protection/100%-% protection)), and calculating the value from a correlation between a plot of the log concentration of compound versus logit activity.

In summary, compounds 5x, 6-7, 9, 13, proved to be highly potent in protecting PC12 cells. The concentration of each analogue required to protect 50% of cells (determined as a PC_{50} value) is shown in Table 1.

Table 1

Concentration of compounds required to induce 50% protection (PC_{50}) of PC_{12} cells from camptothecin–induced cell-death.

Compound (precursor)		PC_{50} nM
5	(PFTα)	252
14	(Z-119)	741
1	(Z-110)	571
15	(Z-113)	728
5x	(Z-117)	306
6	(Z-133)	182
7	(Z-138)	348
8	(Z-139)	418
13	(Z-143)	169
10	(Z-145)	767
4	(Z-135)	379
9	(Z-141)	187
11	(Z-153)	410
16	(Z-1-181)	154
17	(Z-1-163)	93
18	(Z-1-179)	1000
19	(Z-1-165)	315
20	(Z-1-161)	144
21	(Z-1-183)	418
22	(Z-1-175)	327
24	(Z-1-171)	318
25	(Z-1-167)	1100
26	(Z-1-187)	395
2	(Z-1-189)	595
30	(Z-1-169)	133

27	(Z-2-007)	69
28	(Z-2-013)	143
29	(Z-2-035II)	214

In summary, numerous of the analogues (e.g. 5x, 6-7, 9-13, etc.) prove to be highly potent.

Example 5

Neuroprotective Activity of PFTα and its Precursor in Rat Hippocampal Neurons *In Vitro*

2-amino-4,5,6,7-tetrahydrobenzothiazole hydrogen and 1-(4-methylphenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide and their analogues were assessed for their ability to protect rat hippocampal cells in culture from camptothecin (5 μM) or etoposide (5 μM). See Figures 3-5.

Dissociated hippocampal cell cultures were established from embryonic day 18 Sprague-Dawley rats (Harlan, Inc.) as described previously. See Culmsee et al. (2001) *J. Neurochem.* 77:220-28. Cells were grown in polyethyleneimine-coated plastic dishes or 22 mm^2 glass coverslips, and incubated in Neurobasal medium containing B-27 supplements, 2 mM L-glutamine, 25 mg/ml gentamycin, 1 mM Hepes (Gibco BRL) and 0.001% gentamicin sulfate. All experiments were performed using 9-10 day-old cultures. Camptothecin and etoposide (Sigma) were prepared as 500X stocks in DMSO. Neuron survival was quantified by established methods. See Mattson et al. (1993) Neuron 10:243-54. Briefly, viable neurons in premarked fields (10X objective) were counted before experimental treatment and at specified time points thereafter. Neurons with intact neurites of uniform diameter and soma with a smooth round appearance were considered viable. In contrast neurons with fragmented neurites and vacuolated soma were considered non-viable.

The results showed that PFTα (5) possessed potent activity to protect the primary hippocampal cells. At concentrations up to 400 nM, neither PFTα (5) nor its precursor were toxic when administered alone to cells. However, both camptothecin (5

μM) and etoposide (2.5 μM), known to induce neuronal apoptosis by a mechanism involving DNA damage and p53 induction, killed approximately 85% of neurons. Pretreatment of cells with PFTα (5), but not its precursor, resulted in improved cell survival compared to vehicle controls.

The neuroprotective effect of the analogues was also tested. At concentrations of 100 nM none of compounds 14, 1, 15, 5x, 6-11, 13, 16 were toxic when only the analogues were put in the cell. When the hippocampal neurons were pretreated with 100 nM of analogue and then exposed to camptothecin, the neuronal survival for compounds 14, 1, 15, 5x and 5 was 61%, 65%, 23%, 29% and 62% respectively. See Figures 4 and 5. Compounds 14 and 1 had about the same neuroprotective activity as PFTα and exhibited significant neuroprotection against the DNA-damage agent camptothecin. Compound 5x, a 5-methyl substituted derivative of compound 5, and compound 15 could not protect neurons effectively against camptothecin (a topisomerase I inhibitor). When these analogues 14, 1, 15, 5x, 6-11, 13, 16 were tested their ability to prevent neuron against etoposide, compound 14 and compound 1 were more active than compound PFTα, and compound 15 and compound 5x have activity comparable to PFTα. Compounds 14, 1, 15, 5x, and 5 had activity against the topisomerase II inhibitor, etopside.

Compound 14 and compound 1 had neuroprotection against death induced by both camptothecin and etoposide. When these two compounds were selected for further study, they were also shown to suppress caspase activation and protect cultured hippocampal neurons against death induced by glutamate. Neuron survival was increased 133% and 39% respectively when neurons were pretreated with compound 14 or 1.

Thus, compounds 14, 1, 15, 5x, 8 and 9 proved to be highly potency in protecting primary hippocampal cells from apoptosis induced cell death. The N-substituent group of compound 5 proved to be essential for biological action. Modification of N-substituent to omit the carbonyl group, compound 14, resulted in a compound that retained biological activity in the protection of hippocampal cells from both etopside and camptothecin. 4-Methyl substitution in the phenyl position of the N-substituent proved to be non essential for biological action, with compound 13 proving to be highly active in PC12 cells only. Indeed, substitution of a simple alkyl, compound 1, for the

aryl group in the N-substituent was well tolerated to provide high activity in hippocampal cells. Substitution of electron donating (e.g., OCH_3 as in compound 6) and withdrawing (e.g., Cl as in compound 9) groups, particularly in the 4'-position of the phenyl group of the N-substituent, were well tolerated. Methyl substitution in position 5, as in compound **5x**, was well tolerated and provided an agent active in all assays.

Example 6

Neuroprotective Activity of PFTα (2) and its Precursor in an I*n Vivo* Stroke Model

Surgery was performed in anesthetized (xylazine 5 mg/kg, chloral hydrate 350 mg/kg) mice (3 month old C57Bl/6) in accordance with a protocol approved by the NIH Animal Care and Use Committee. The focal ischemia/reperfusion model has been described previously. See Bruce et al. (1996) *Nat. Med.* 2:788-94. This method involves occluding the middle cerebral artery for 1 h with a nylon thread, and then removing it to allow reperfusion. During the procedure, mice were maintained at 37°C and blood gases, flow and pressure were monitored. At 24 h after ischemia, mice were anesthetized, decapitated, and their brains were cut into 2 mm coronal sections, which then were stained with triphenyltetrazolium for 30 min at 37°C. Images of the stained brains were captured by digital camera for quantitative analysis of infarct area and volume.

PFTα (5) (2 mg/kg, i.p. in 0.2% DMSO) administered 30 min prior to the initiation of cerebral ischemia exhibited neuroprotective activity. Figure 6A shows the infarct area at four different brain levels, with a reduction in the infarct area following PFTα. The infarct volume for vehicle was 40 mm^3. When mice were treated with PFTα, infarct volume was 20 mm^3, a highly significant 50% decrease. See Figure 6B. Thus, after systemic administration, PFTα entered and acted in the brain.

Example 7

Neuroprotective Activity of PFTα and its Analogues in an *In Vivo* Model of Parkinson's Disease

The ability of PFTα (5) and compounds 5x (Z-1-117) and 13 (Z-1-143) to protect dopaminergic neurons against MPTP toxicity was tested. MPTP (20 mg/kg) was administered intraperitoneally to 2 month-old male C57BL/6 mice by four injections at two hour intervals to induce dopaminergic cell death. Animals were pretreated with either PFTα (2mg/kg), compound 5x (2mg/kg), compound 13 (2mg/kg), or vehicle (0.2% DMSO) by intraperritoneal injection 30 min. prior to the first MPTP injection and 30 min. after the last MPTP injection.

At seven days, behavioral tests were performed using the rotarod test equipment. The number of falls and running times were measured. See Figure 7. Treatment with PFT-α and compound 5x resulted in a statistically significant decease in the number of falls caused by MPTP treatment. See Figure 7A. Also, PFT-α and compound 5x resulted in a statistically significant increase in the running time, which is markedly reduced by MPTP treatment as compared to control. See Figure 7B.

Levels of tyrosine hydroxylase (TH), the enzyme that catalyzes the rate-limiting step in dopamine synthesis, also were assessed in the striatum using Western blot analysis. See Figure 8. Densitometric analysis shows that PFT-α and compound 5x reverse the MPTP reduction in TH levels.

In a separate experiment, levels of striatal dopamine, dopamine metabolites, serotonin, and serotonin metabolites were measured using HPLC analysis. Specifically, mice were euthanatized, and striatal tissue samples were removed and levels of dopamine, DOPAC, HVA, 5-HT, 5-HIAA were quantified. The data are shown in Table 2. PFT-α and compound (5x) resulted in a statistically significant increase in levels of dopamine, DOPAC, and HVA as compared to the MPTP-induced reduction over control. There was no significant difference in levels of serotonin or serotonin metabolites.

Table 2

	Dopamine	DOPAC	HVA	5-HT	5-HIAA
Control	6178 ± 799	337 ± 42	618 ± 53	486 ± 33	298 ± 29
MPTP	405 ± 56	undetectable	124 ± 53	441 ± 22	239 ± 24
Vehicle+ MPTP	404 ± 93	undetectable	125 ± 37	406 ± 17	243 ± 18
PFT-α (5)+ MPTP	3314 ± 670**	170 ± 25 **	328 ± 35**	419 ± 20	245 ± 33
Z-1-117 (5x)+ MPTP	1833 ± 256*	102 ± 11 **	302 ± 20**	424 ± 12	246 ± 15
Z-1-143 (13)+ MPTP	440 ± 122	10 ± 10	91 ± 58	429 ± 42	223 ± 45

Values (pg/mg tissue weight) are the mean ± SE of determinations made in 4-6 mice/group.

*$P<0.05$, **$P<0.01$ compared to the value of MPTP group. ANOVA with Scheffe post-hoc tests.

In yet another experiment, the number of TH-immunostained cells in the substantia nigra was assessed in four animals seven days after treatment. Mice were euthanized and perfused by 4% paraformadehyde transcardially. Brain sections were

cut and immunostained with an antibody against TH. PFT-α and compound 5x attenuated MPTP-induced loss of substantia nigra dopaminergic neurons. See Figure 9.

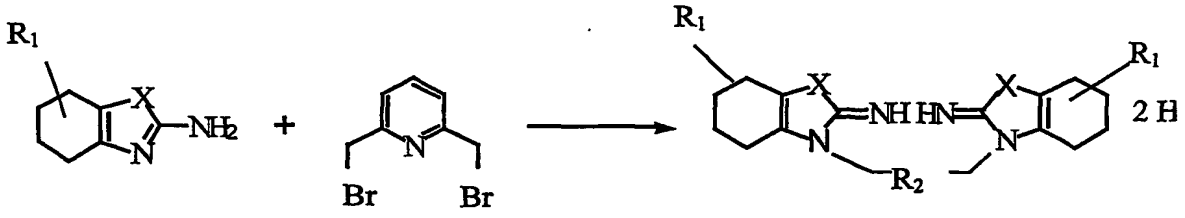
Example 8

Neuroprotective Activity of PFT Analogues to an Excitotoxic Insult

Primary hippocampal neurons were prepared and cultured as described above. Cultures were pretreated with compounds 14 and 1 (0.04 μM) 1h before exposure to glutamate (20μM) in Locke's medium. The percentage of neuronal survival 24h after the onset of insult is given as mean values ± SD. Glutamate resulted in a marked decrease in neuronal survival. The glutamate-induced decrease was at least partially reversed by compound 14, thus demonstrating a neuroprotective effect. See Figure 10.

Example 9

Scheme B



(XV)

Z-1-169: 2,6-Bis[(4,5,6,7-tetrahydro-2-imino-3(2*H*)-benzothiazolyl)methyl]pyridine dihydrobromide (30)

This was prepared by a similar procedure from 2-amino-4,5,6,7-tetrahydrobenzothiazole (109 mg, 0.7 mmol) and 2,6-Bis(bromomethyl)pyridine (95 mg, 0.35 mmol); yield (61%); ^{1}H NMR (DMSO-d_6) δ 9.29 (s, 2H), 7.96 (t, J = 7.7 Hz,

1H), 7.47 (d, J = 7.7Hz, 2H), 5.33 (s, 4H), 2.56 (m, 4H), 2.12 (m, 4H), 1.68 (m, 8H); Anal. ($C_{21}H_{27}Br_2N_5S_2$) C, H, N.

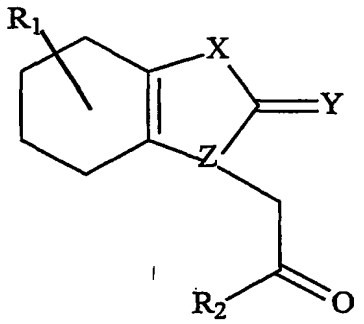
In formula (XV) above, R_1 is H, C_{1-8} alkyl or aryl, substituted or unsubstituted; R_2 is any aromatic ring, substituted or unsubstituted and X is S or O.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A tetrahydrobenzothiazole analogue having the formula (I):



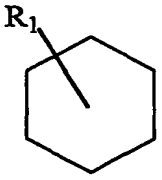
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;

 = is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the

group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

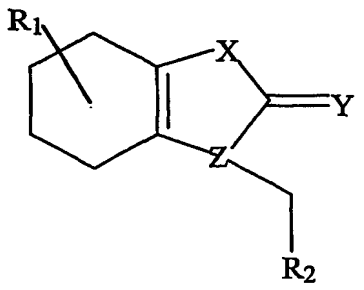
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

2. A pharmaceutical composition comprised of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

3. A tetrahydrobenzothiazole analogue having the formula (II):



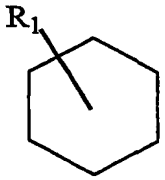
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

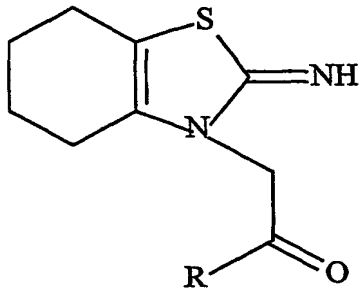
(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

4. A pharmaceutical composition comprised of a compound of claim 3 in combination with a pharmaceutically acceptable carrier.

5. A tetrahydrobenzothiazole analogue having the formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl;

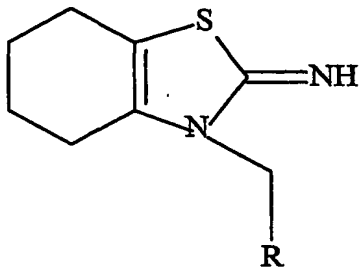
(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O,

OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

6. An analogue of claim 5,wherein R is ethyl, methoxy, methoxyphenyl, fluorophenyl, chlorophenyl, nitrophenyl, or tetradecyloxyphenyl.

7. A pharmaceutical composition comprised of a compound of claim 5 in combination with a pharmaceutically acceptable carrier.

8. A tetrahydrobenzothiazole analogue having the formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

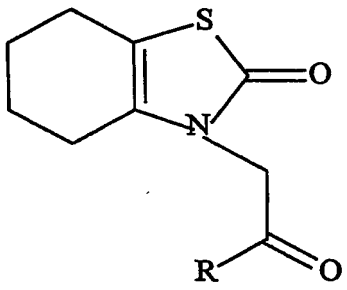
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

9. An analogue of claim 8,wherein R is benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

10. A pharmaceutical composition comprised of a compound in accordance with claim 8 in combination with a pharmaceutically acceptable carrier.

11. A tetrahydrobenzothiazole analogue having the formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

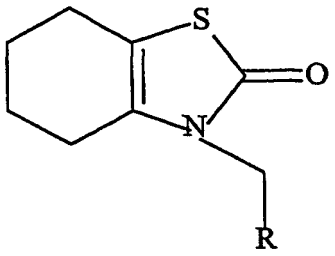
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

12. An analogue of claim 11,wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

13. A pharmaceutical composition comprised of a compound in accordance with claim 11 in combination with a pharmaceutically acceptable carrier.

14. A tetrahydrobenzothiazole analogue having the formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

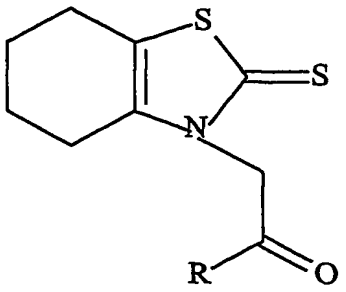
(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

15. An analogue of claim 14, wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

16. A pharmaceutical composition comprised of a compound in accordance with claim 14 in combination with a pharmaceutically acceptable carrier.

17. A tetrahydrobenzothiazole analogue having the formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

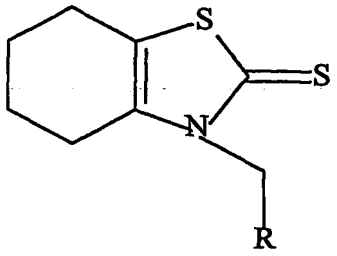
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

18. An analogue of claim 17, wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

19. A pharmaceutical composition comprised of a compound in accordance with claim 17 in combination with a pharmaceutically acceptable carrier.

20. A tetrahydrobenzothiazole analogue having the formula (VIII):



(VIII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

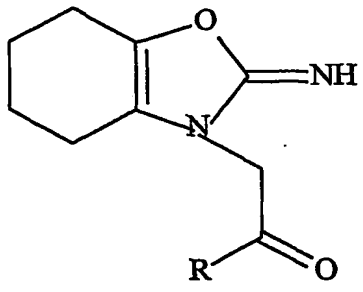
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

21. An analogue of claim 20, wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

22. A pharmaceutical composition comprised of a compound in accordance with claim 20 in combination with a pharmaceutically acceptable carrier.

23. A tetrahydrobenzooxyzole analogue having the formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

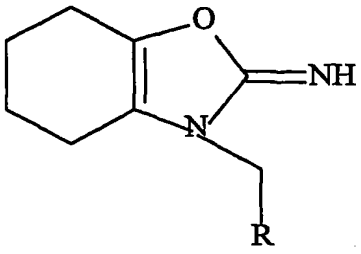
(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

24. An analogue of claim 23, wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

25. A pharmaceutical composition comprised of a compound in accordance with claim 23 in combination with a pharmaceutically acceptable carrier.

26. A tetrahydrobenzooxyzole analogue having the formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

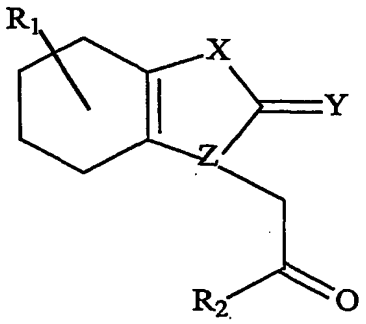
27. An analogue of claim 26, wherein R is methyl, benzyl, cyclopropylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, dichlorobenzyl, methylbenzyl, t-butylbenzyl, nitrobenzyl, cyanobenzyl, trifluoromethylbenzyl, phenylbenzyl, menaphthyl, phenylethyl, or butyl.

28. A pharmaceutical composition comprised of a compound in accordance with claim 26 in combination with a pharmaceutically acceptable carrier.

29. A method of reducing or delaying apoptosis in a population of cells, comprising contacting the population of cells with a tetrahydrobenzothiazole analogue, thereby reducing or delaying apoptosis in the population of cells.

30. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises pifithrin-α.

31. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (I):



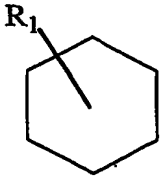
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

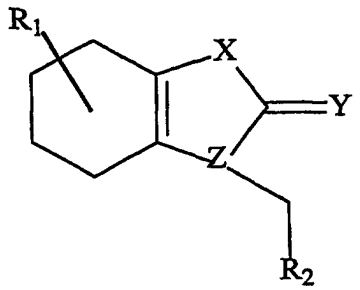
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

32. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (II):



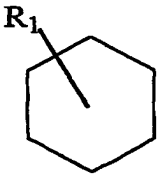
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;

 = is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

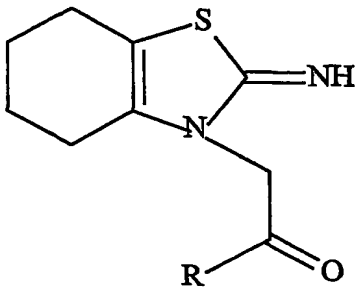
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

33. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

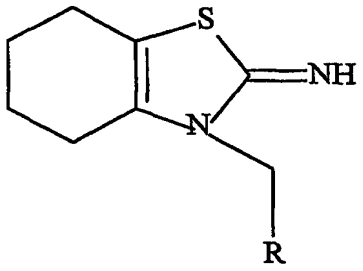
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl;

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

34. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting

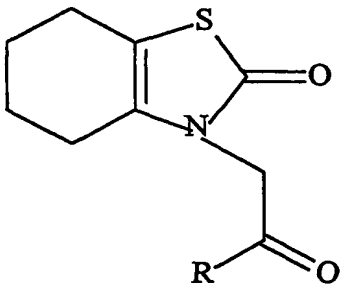
of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

35. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

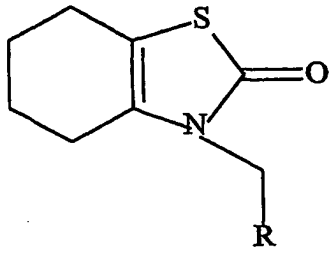
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

36. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

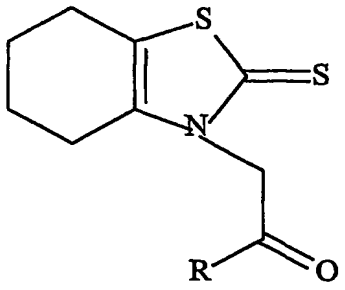
R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

37. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

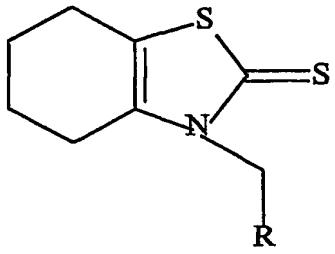
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

38. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VIII):



(VIII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting

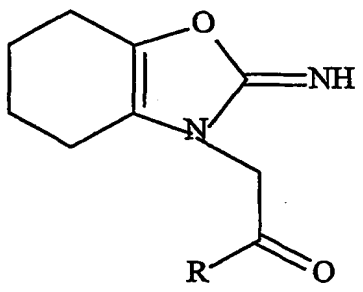
of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

39. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member

selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

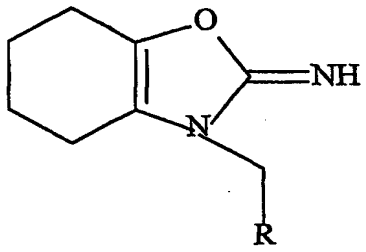
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

40. The method of claim 29, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

41. The method of claim 29, wherein the contacting step is *in vivo*.

42. The method of claim 29, wherein the contacting step is *in vitro*.

43. The method of claim 29, wherein the cells are neural cells.

44. The method of claim 43, wherein the neural cells are neuronal cells.

45. The method of claim 29, wherein the cells are cardiac cells.

46. The method of claim 45, wherein the cells are cardiomyocytes.

47. The method of claim 29, wherein the cells are muscle cells.

48. The method of claim 47, wherein the muscle cells are skeletal muscle cells.

49. The method of claim 29, wherein the cells are pancreatic islet cells.

50. The method of claim 29, wherein the apoptosis is induced by a toxin.

51. The method of claim 29, wherein the apoptosis is induced by an environmental factor.

52. The method of claim 29, wherein the apoptosis is induced by a degenerative condition.

53. The method of claim 29, wherein the apoptosis is induced by a severe seizure disorder.

54. The method of claim 29, wherein the apoptosis is induced by a genetic disease.

55. The method of claim 50, wherein the toxin is selected from the group consisting of a neurotoxic form of amyloid β-peptide, camptothecin, glutamate, etoposide, anti-cancer drugs, vinca alkaloids, 3-nitrognognonic acid, MPTP, domoic acid, and kainic acid.

56. The method of claim 29, wherein the apoptosis is induced by ischemia.

57. The method of claim 52, wherein the ischemia is induced by a stroke.

58. The method of claim 42, wherein the ischemia is induced by a myocardial infarction.

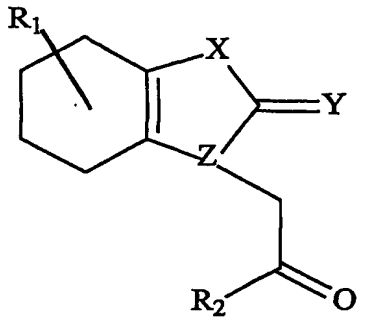
59. The method of claim 29, wherein the apoptosis is induced by trauma.

60. The method of claim 29, wherein the apoptosis is induced by a genetic defect.

61. A method of treating a subject with a degenerative condition or of reducing one or more symptons of a degenerative condition in a subject, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue.

62. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises pififthrin-α.

63. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (I):



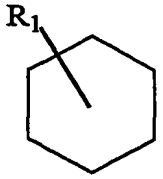
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

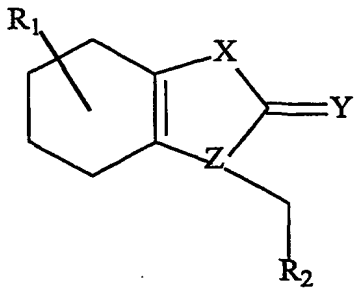
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

64. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (II):



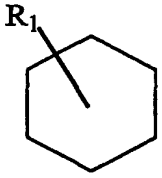
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

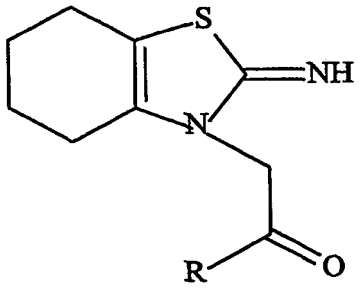
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

65. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

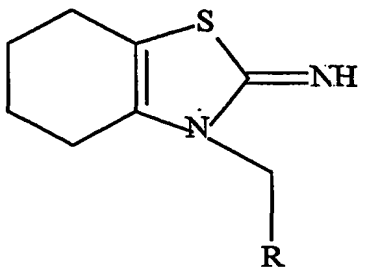
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl;

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

66. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member

selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

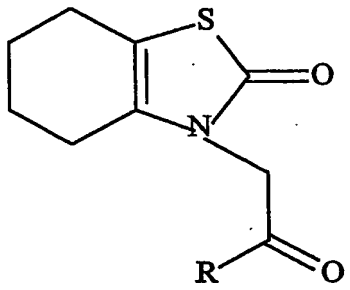
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

67. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

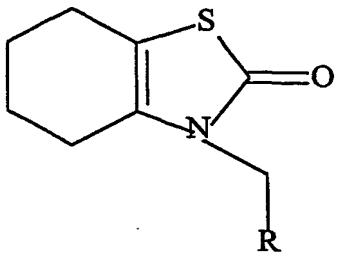
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

68. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

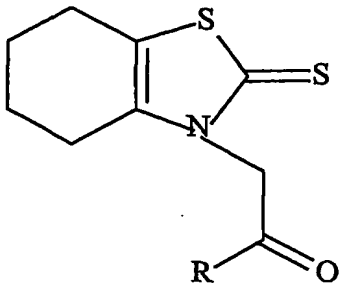
R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

69. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

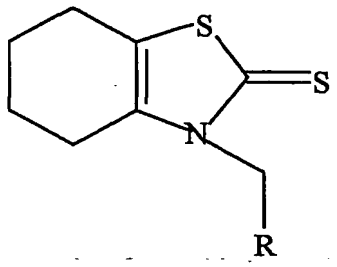
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

70. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VIII):



(VIII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

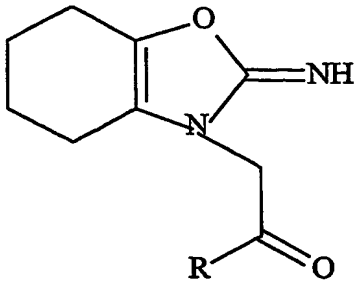
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH,

halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

71. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

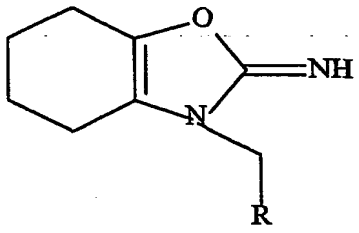
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

72. The method of claim 57, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

73. The method of claim 57, wherein the degenerative condition is a neurodegenerative condition.

74. The method of claim 69, wherein the neurodegenerative condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, multiple sclerosis, brain injury, spinal cord injury, and peripheral neuropathy.

75. The method of claim 57, wherein the degenerative condition is a degenerative cardiomyopathy.

76. The method of claim 57, wherein the degenerative condition is a degenerative myopathy.

77. The method of claim 57, wherein the degenerative condition is diabetes.

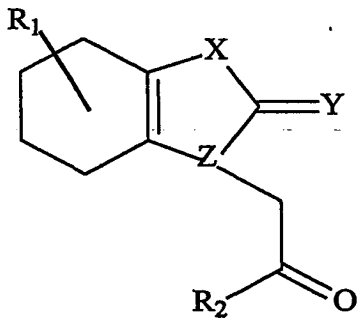
78. The method of claim 57, wherein the subject is a human.

79. A method of treating a subject after an ischemic event to reduce ischemia-induced apoptosis, comprising administering to the subject a therapeutically

effective amount of a tetrahydrobenzothiazole analogue, thereby reducing apoptosis.

80. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises pififthrin-α.

81. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (I):



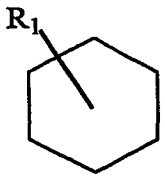
(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member

selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

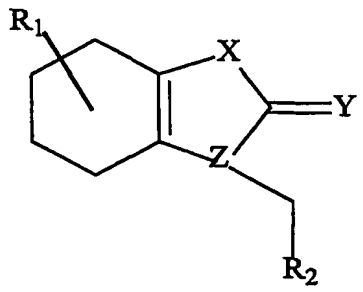
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

82. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (II):



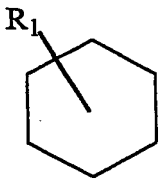
(II)

or a pharmaceutically acceptable salt or ester thereof, wherein:

X is O or S;

Y is NH, O, NR_2 or S;

Z is N or CH;



= is a mono-substituted, di-substituted, tri-substituted, or quad-substituted 6-member ring that is saturated or unsaturated, wherein the R_1 substituents are independently chosen from H, CN, NO2, S, N, O, OH, COOH, halogen, and R_2, but not methyl ; and

R_2 is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

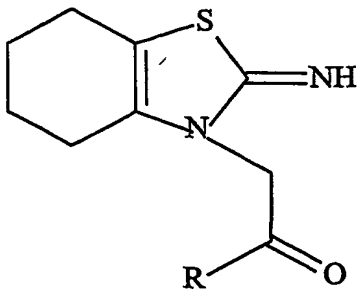
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

83. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (III):



(III)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of one carbon atom or from 3 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

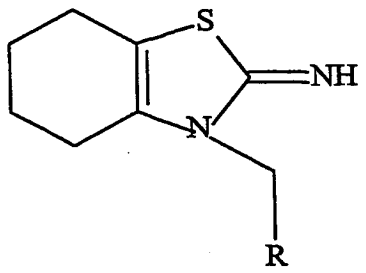
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_2-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy, wherein the halogen is not in the para position;

(d) bisaryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl;

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O,

OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

84. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IV):



(IV)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

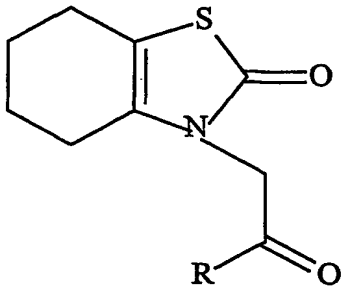
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

85. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (V):



(V)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

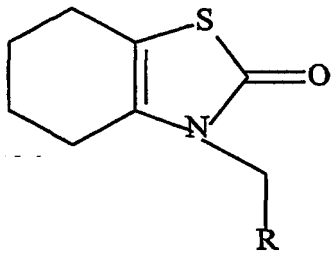
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH,

halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

86. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VI):



(VI)

or a pharmaceutically acceptable salt or ester thereof, wherein:

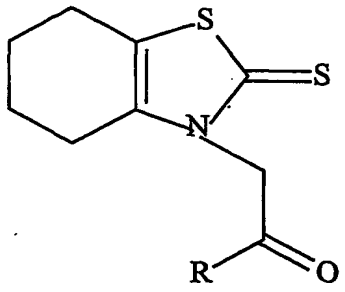
R is selected from the group consisting of:

(a) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(b) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(c) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

87. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VII):



(VII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

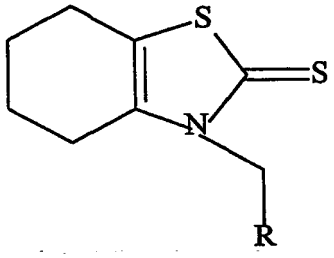
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

88. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (VIII):



(VIII)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

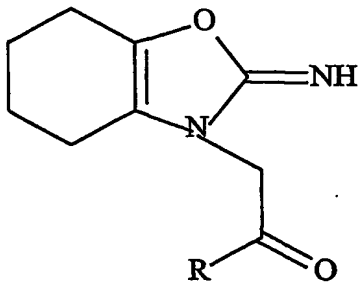
(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH,

halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

89. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (IX):



(IX)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

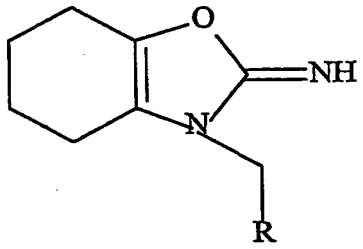
(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

90. The method of claim 75, wherein the tetrahydrobenzothiazole analogue comprises one or more analogues of formula (X):



(X)

or a pharmaceutically acceptable salt or ester thereof, wherein:

R is selected from the group consisting of:

(a) alkyl, or alkenyl, or alkynyl, each of which are straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, OH, COOH, and halogen;

(b) alkoxy which is straight chain, branched chain or cyclic, having a carbon chain length of from 1 to 20 carbon atoms, unsubstituted or substituted with at least one member selected from the group consisting

of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, and C_1-C_{20} alkynyl;

(c) aryl which is substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, and C_1-C_{20} alkoxy;

(d) bisaryl which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl; and

(e) condensed aromatic which is unsubstituted or substituted with at least one member selected from the group consisting of CN, NO_2, S, N, O, OH, COOH, halogen, C_1-C_{20} alkyl, C_1-C_{20} alkenyl, C_1-C_{20} alkynyl, C_1-C_{20} alkoxy, and aryl.

91. The method of claim 75, wherein the ischemic event is a stroke.

92. The method of claim 75, wherein the ischemic event is a myocardial infarction.

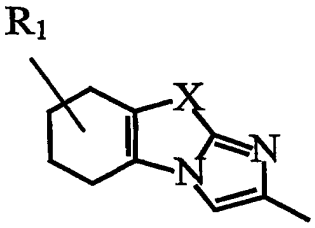
93. The method of claim 75, wherein the subject is a human.

94. A tetrahydrobenzothlazole analogue wherein the analogue is
Ethyl 2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-acetate hydrobromide,
3-(phenylmethyl)-4,5,6,7-tetrahydro-2(3*H*)-benzothiazolimine hydrobromide,
1-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-2-butanone hydrobromide,
3-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2(3*H*)-benzothiazolimine hydrobromide,
1-(4-methylphenyl)-2-(4,5,6,7-tertahydro-2-imino-6-methyl-3(2*H*)-benzothiazolyl)-ethanone hydrobromide,
1-(4-methylphenyl)-2-(4,5,6,7-tertahydro-2-imino-6-methyl-3(2*H*)-benzothiazolyl)-ethanone hydrobromide,

1-(2-methoxylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide,
1-(3-methoxylphenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide,
1-phenyl-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide, or
1-(4-chlorophenyl)-2-(4,5,6,7-tertahydro-2-imino-3(2*H*)-benzothiazolyl)-ethanone hydrobromide.

95. A pharmaceutical composition comprised of a compound in accordance with claim 90 in combination with a pharmaceutically acceptable carrier.

96. A method of treating a subject with a degenerative condition or of reducing one or more symptoms of a degenerative condition in a subject, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue of the formula XIV

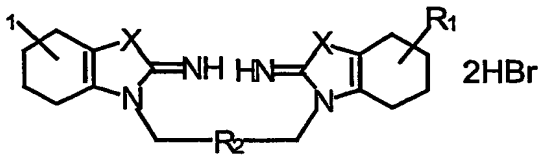


(XIV)

or a pharmaceutically acceptable salt or ester thereof, wherein

R_1 is H, or CH_3, R_2 is C_{1-8} alkyl or aryl substituted or unsubstituted and X is S or O.

97. A tetrahydrobezothaizole analogue having the formula (XV)



(XV)

or a pharmaceutically acceptable salt or ester thereof, wherein
R_1 is H, C1-8 alkyl or aryl substituted or unsubstituted, R_2 is any aromatic ring substituted or unsubstituted and X is S or O.

98. A pharmaceutical composition comprised of a compound of claim 97 in combination with a pharmaceutical acceptable carrier.

99. A method of treating a subject with a degenerative condition or of reducing one or more symptoms of a degenerative condition in a subject, comprising administering to the subject a therapeutically effective amount of the tetrahydrobenzothiazole analogue of claim 97.

100. A method of treating a subject exposed to irradiation, comprising administering to the subject a therapeutically effective amount of a tetrahydrobenzothiazole analogue

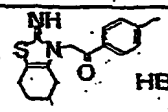
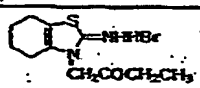
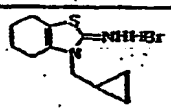
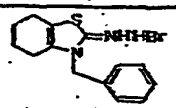
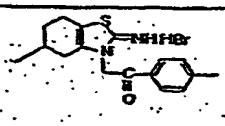
	Ref. No.	Structure	Mol. Wt.	^{1}H-NMR	m.p.	Solubility
	Z-1-073		367.3049	Z-1-073 ^{13}C NMR		
1	Z-1-110		305.2356	Z-1-110		Water
15	Z-1-113		289.2362	Z-1-113		Water
14	Z-1-119		325.2683	Z-1-119		Water
5X	Z-1-117		381.3315	Z-1-117		Hot water

Fig. 1

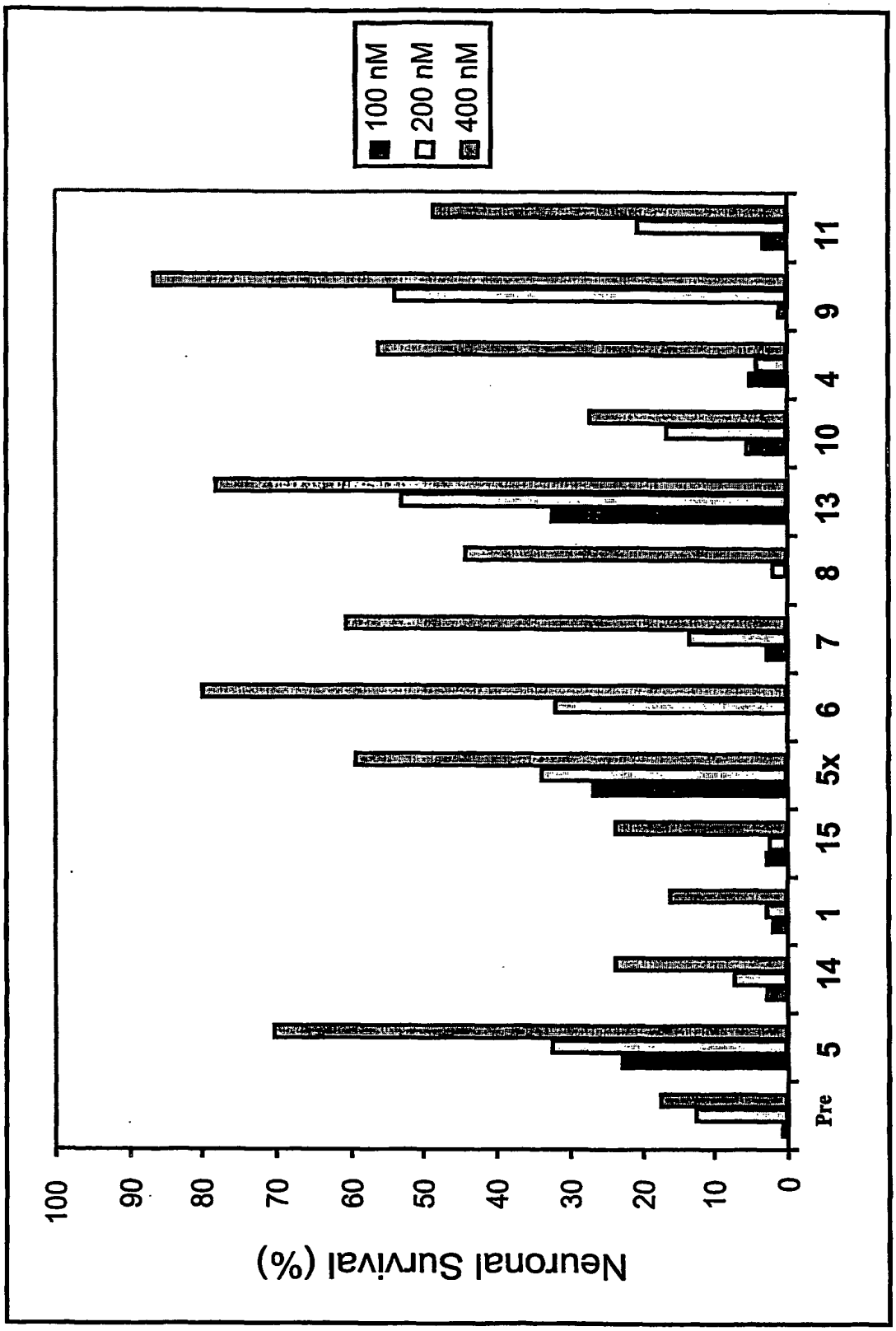

100 nM
200 nM
400 nM
Neuronal Survival (%)
0
10
20
30
40
50
60
70
80
90
100
Pre
5
14
1
15
5x
6
7
8
13
10
4
9
11

Fig. 2a

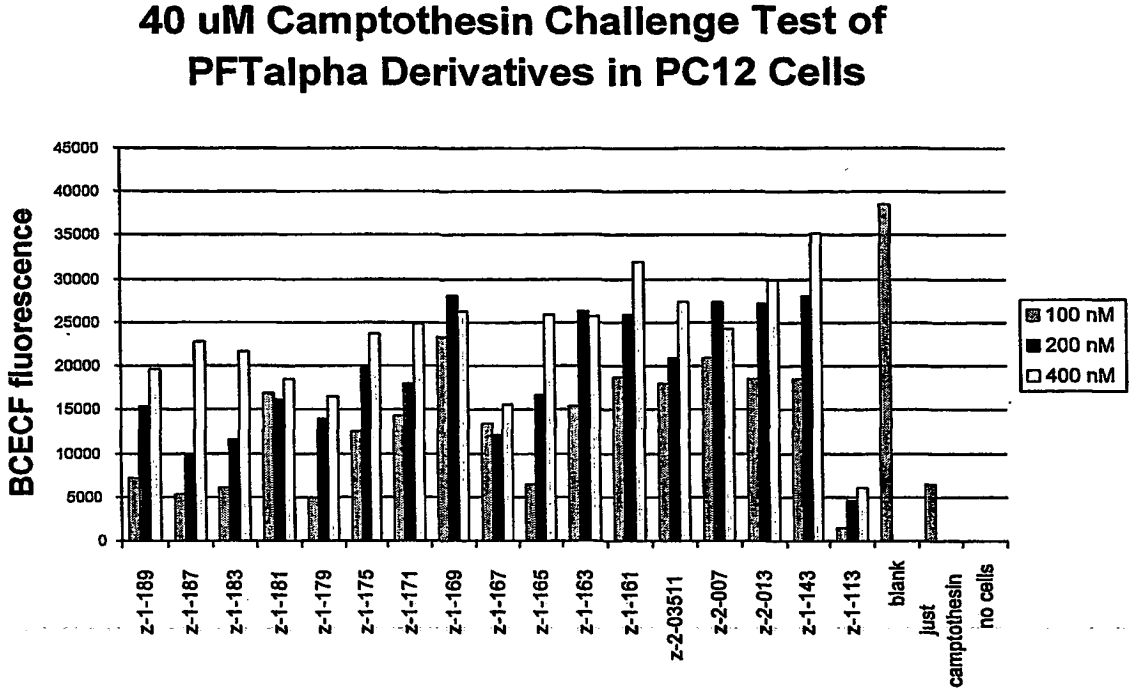

40 uM Camptothesin Challenge Test of PFTalpha Derivatives in PC12 Cells
BCECF fluorescence
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
100 nM
200 nM
400 nM
z-1-189
z-1-187
z-1-183
z-1-181
z-1-179
z-1-175
z-1-171
z-1-169
z-1-167
z-1-165
z-1-163
z-1-161
z-2-03511
z-2-007
z-2-013
z-1-143
z-1-113
blank
just camptothesin
no cells

Fig. 2b

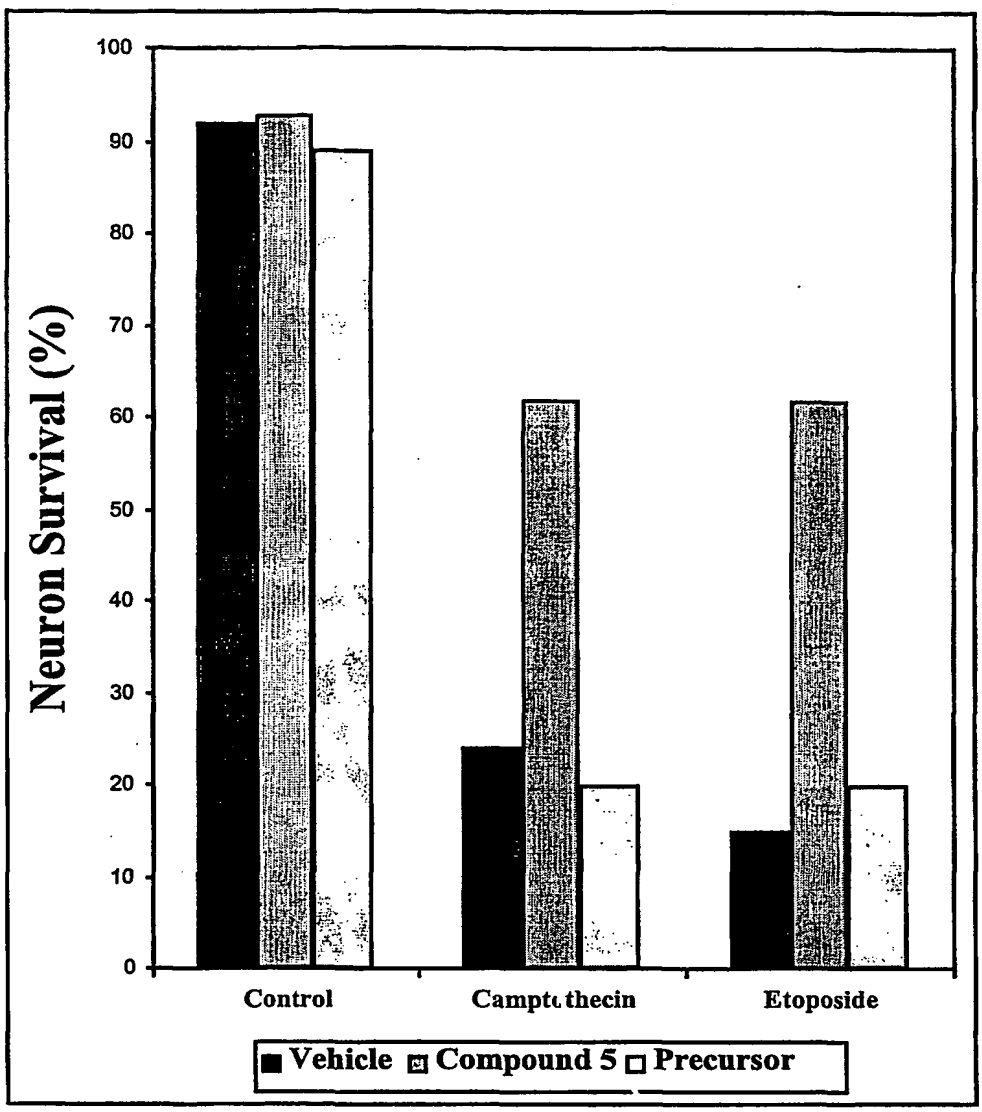

Neuron Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Control
Camptothecin
Etoposide
Vehicle
Compound 5
Precursor

Fig. 3

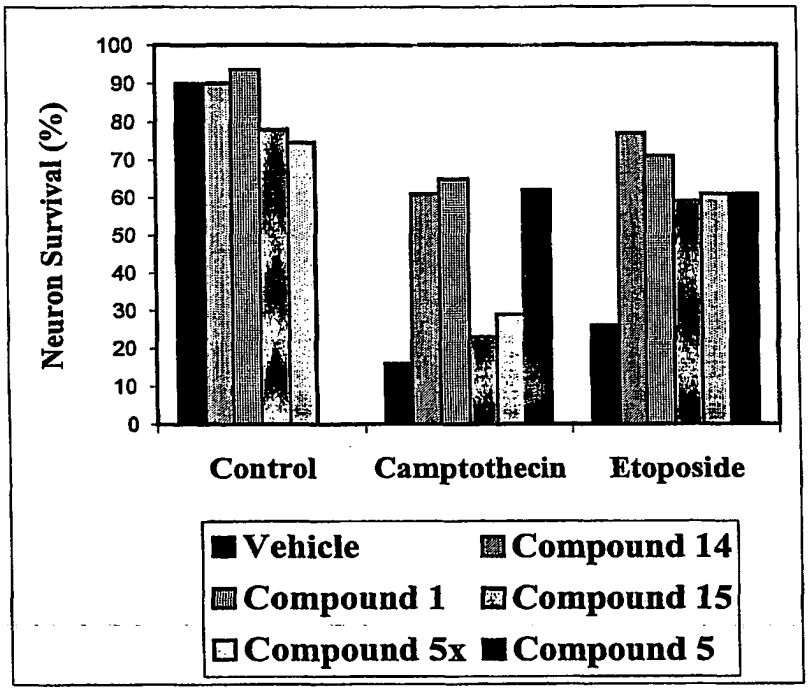

Neuron Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Control
Camptothecin
Etoposide
Vehicle
Compound 14
Compound 1
Compound 15
Compound 5x
Compound 5

Fig. 4

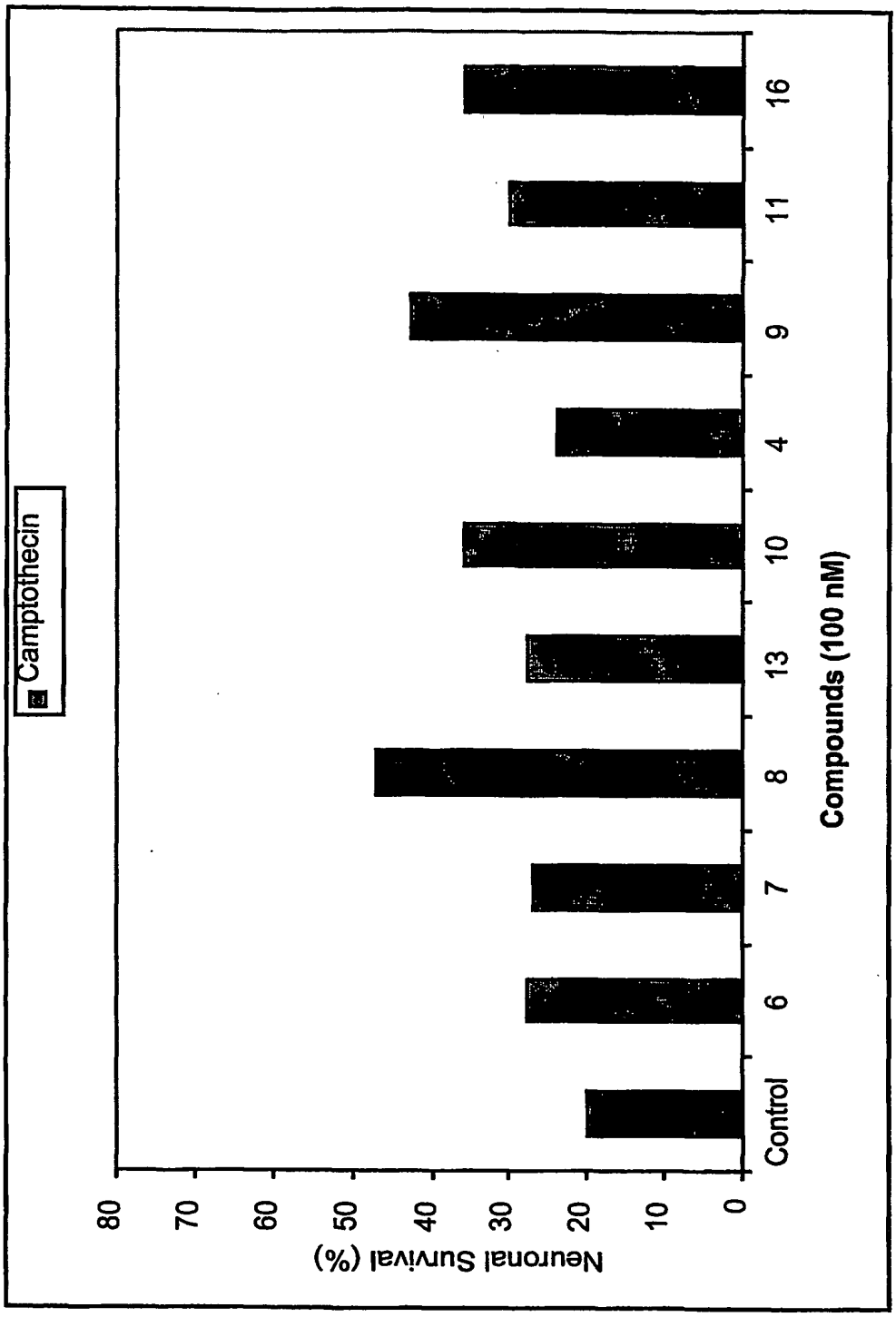

Camptothecin
Neuronal Survival (%)
0
10
20
30
40
50
60
70
80
Control
6
7
8
13
10
4
9
11
16
Compounds (100 nM)

Fig. 5

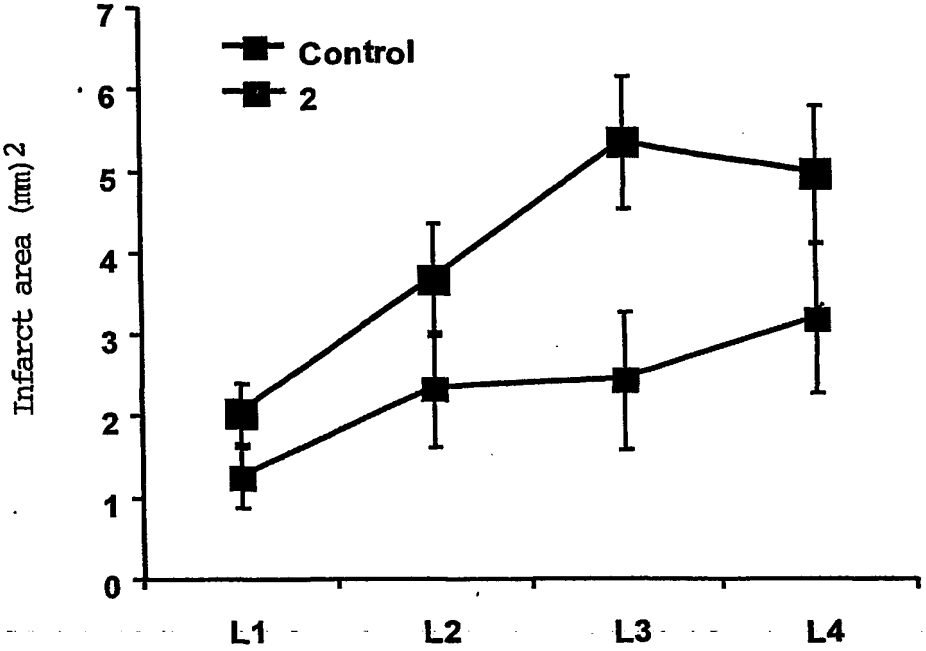

Control
2
Infarct area (mm)2
0
1
2
3
4
5
6
7
L1
L2
L3
L4

Fig. 6a

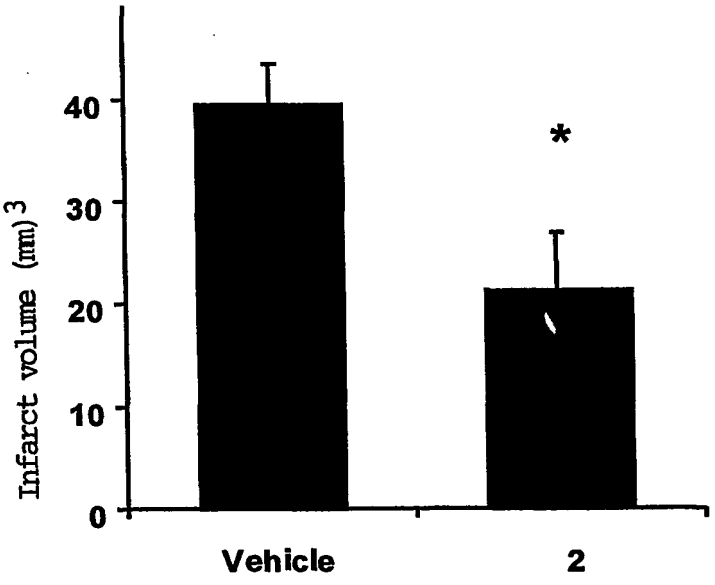

Infarct volume (mm)3
0
10
20
30
40
*
Vehicle
2

Fig. 6b

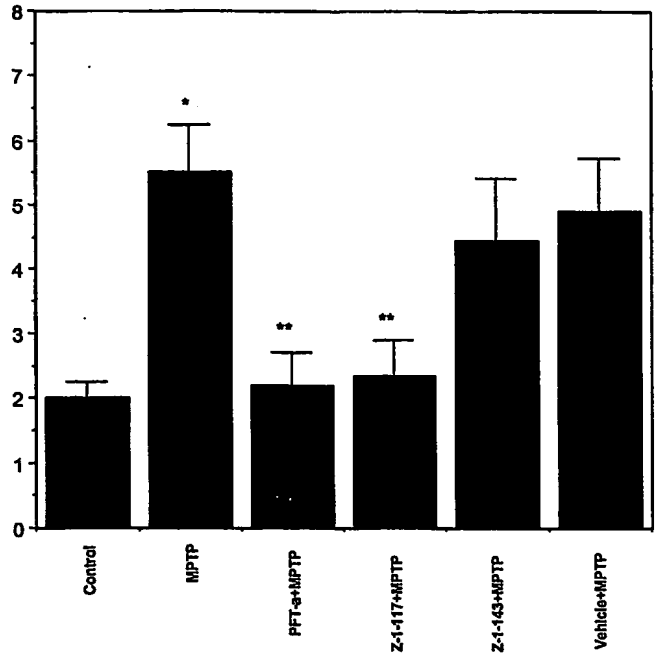

8
7
6
5
4
3
2
1
0
*
**
**
Control
MPTP
PFT-α+MPTP
Z-1-117+MPTP
Z-1-143+MPTP
Vehicle+MPTP

Fig. 7a

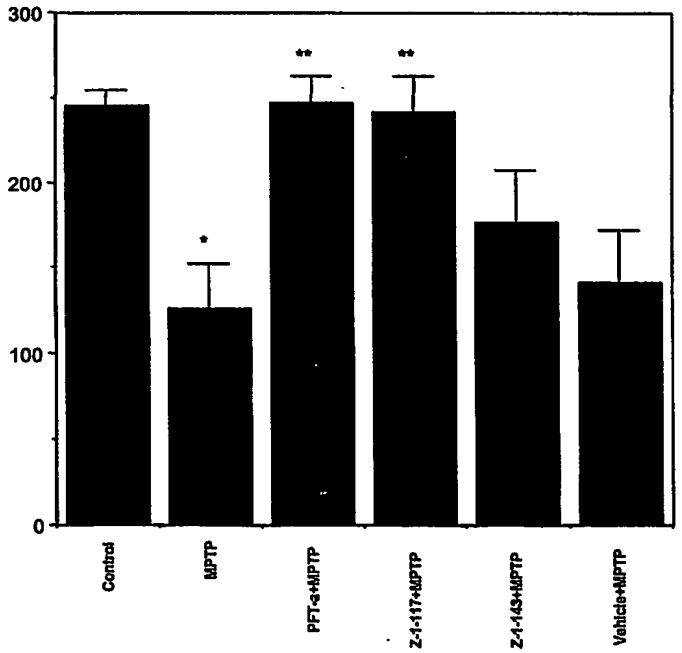

300
200
100
0
**
**
*
Control
MPTP
PFT-α+MPTP
Z-1-117+MPTP
Z-1-143+MPTP
Vehicle+MPTP

Fig. 7b

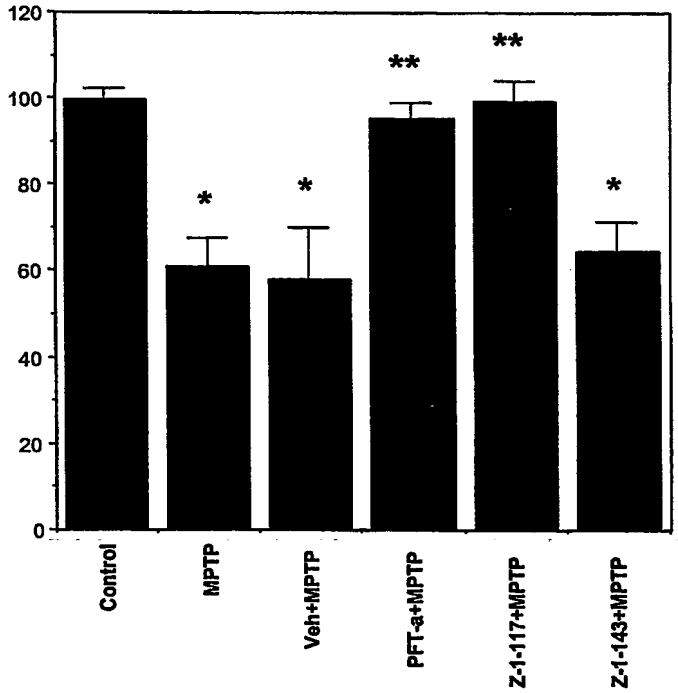

120
100
80
60
40
20
0
*
*
**
**
*
Control
MPTP
Veh+MPTP
PFT-α+MPTP
Z-1-117+MPTP
Z-1-143+MPTP

Fig. 8

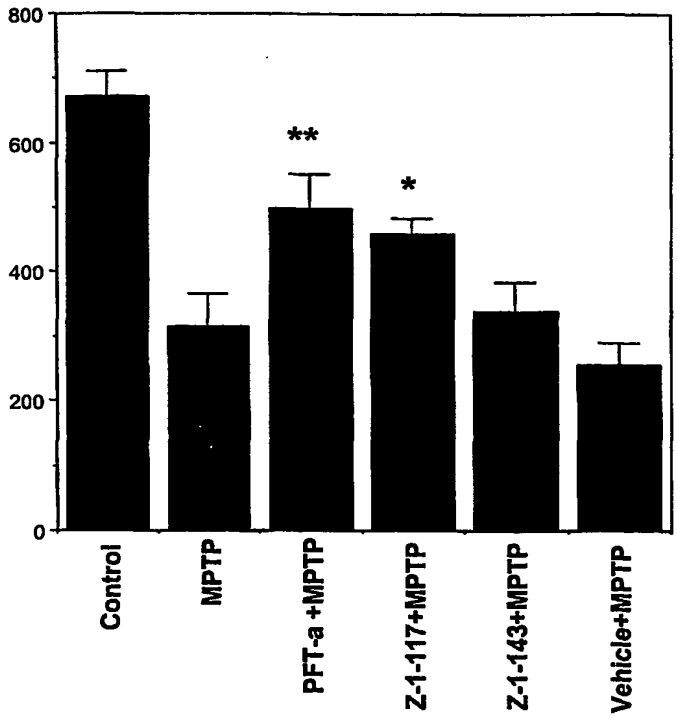

800
600
400
200
0
**
*
Control
MPTP
PFT-a +MPTP
Z-1-117+MPTP
Z-1-143+MPTP
Vehicle+MPTP

Fig. 9

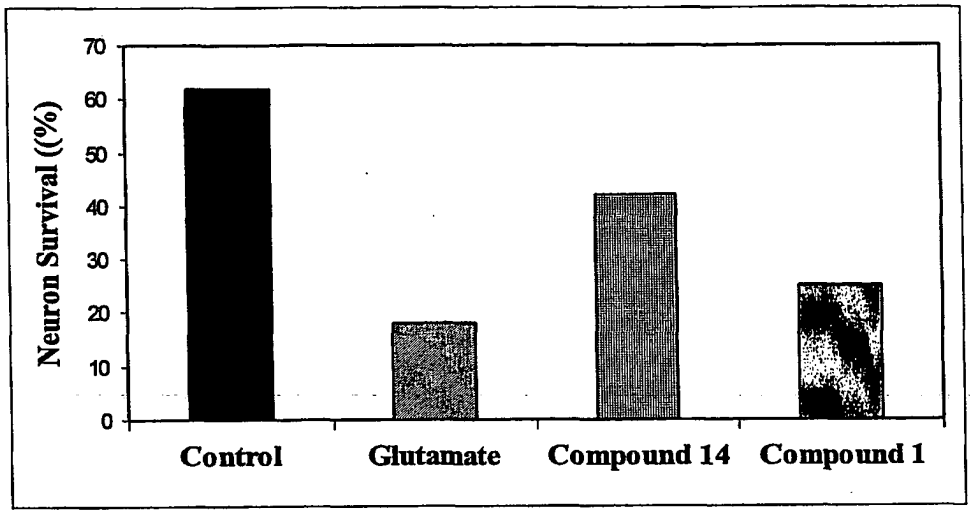

Neuron Survival ((%)
70
60
50
40
30
20
10
0
Control
Glutamate
Compound 14
Compound 1

Fig. 10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Filed on 6 July 2000 (06.07.2000)

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(72) Inventor *(for all designated States except US)*: **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; c/o National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US).

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(75) Inventors/Applicants *(for US only)*: **GREIG, Nigel, H.** [US/US]; 11 Anne Brent Garth, Phoenix, MD 21131 (US). **MATTSON, Mark** [US/US]; 858 E. Wheel Road, Bel Air, MD 21015 (US). **ZHU, Xiaoxiang** [US/US]; 6114 East Pratt Street, Baltimore, MD 21224 (US). **YU, Qian-Sheng** [CN/US]; 116 Ridgefield, Lutherville, MD 21093 (US). **HOLLOWAY, Harold, Wayne** [US/US]; 121 Mariners Point Dr., Middle River, MD 21220 (US).

(74) Agents: **MILLER, Mary, L.** et al.; Needle & Rosenberg, P.C., Suite 1200, The Candler Building, 127 Peachtree Street, N.E., Atlanta, GA 30303-1811 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
18 July 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/004409 A3

(54) Title: TETRAHYDROBENZOTHIAZOLE ANALOGUES AS NEUROPROTECTIVE AGENTS

(57) Abstract: This invention relates generally to tetrahydrobenzothiazole analogues and tetrahydrobenzooxyzole analogues, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to methods of treatment using these compounds. The invention also encompasses pharmaceutically acceptable esters, amides, and salts of such compounds. The invention further provides a method of reducing or delaying apoptosis in a population of cells, comprising contacting the population of cells with a tetrahydrobenzothiazole analogue or a tetrahydrobenzooxyzole analogue, thereby reducing or delaying apoptosis in the population of cells.

INTERNATIONAL SEARCH REPORT

Ir ıational Application No
PCT/US 01/21504

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/82 C07D277/68 C07D277/72 C07D263/58 C07D513/04
C07D498/04 A61K31/428 A61K31/423 A61P25/00 A61P25/16
A61P25/28 //(C07D513/04,277:00,235:00),(C07D498/04,263:00,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOMAROV P G ET AL: "A CHEMICAL INHIBITOR OF P53 THAT PROTECTS MICE FROM THE SIDE EFFECTS OF CANCER THERAPY" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5434, 10 September 1999 (1999-09-10), pages 1733-1737, XP000953397 ISSN: 0036-8075 cited in the application page 1733, abstract; page 1734, column 1, line 3 to page 1735, column 3, line 4; page 1735, column 3, last line to page 1737, column 1, line 11; page 1737, column 1, bridge paragraph to column 2 --- -/--	1-95,100

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2002	22/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

5

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ·ational Application No
PCT/US 01/21504

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 186 087 A (THOMAE GMBH DR K) 2 July 1986 (1986-07-02) claims 1,8-11	61
X	DE 39 23 689 A (BOEHRINGER INGELHEIM KG) 24 January 1991 (1991-01-24) page 3, line 48 - line 56; claims 1,6	61
X	US 3 462 448 A (KELYMAN JACQUELINE S) 19 August 1969 (1969-08-19) column 2, line 71 -column 3, line 25; claims 1,3	61
X	DE 19 26 558 A (DR. KARL THOMAE GMBH) 3 December 1970 (1970-12-03) claims 1,7,8	61

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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°L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

°O° document referring to an oral disclosure, use, exhibition or other means

°P° document published prior to the international filing date but later than the priority date claimed

°T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

°X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

°Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

°&° document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

5

Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO_____0204409A3_I_>

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 42 41 013 A (BOEHRINGER INGELHEIM KG) 9 June 1994 (1994-06-09) claims	61
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 11, 30 September 1998 (1998-09-30) & JP 10 152488 A (TOKYO TANABE CO LTD), 9 June 1998 (1998-06-09) abstract	61
X	PATENT ABSTRACTS OF JAPAN vol. 1996, no. 09, 30 September 1996 (1996-09-30) & JP 08 113570 A (SANKYO CO LTD;SANKYO KASEI KOGYO KK), 7 May 1996 (1996-05-07) abstract	61
X	US 4 769 370 A (WOLTERSDORF JR OTTO W ET AL) 6 September 1988 (1988-09-06) abstract	61
A	EP 0 705 832 A (LILLY INDUSTRIES LTD) 10 April 1996 (1996-04-10) page 8, line 15 - line 24; claims 1,7,8	1-100
A	EP 0 281 261 A (LUNDBECK & CO AS H) 7 September 1988 (1988-09-07) page 2, line 1 - line 5; claims 1,4	1-100
A	US 4 377 695 A (LAUTENSCHLAEGER HANS-HEINER ET AL) 22 March 1983 (1983-03-22) column 1, line 15 - line 63	1-100
A	US 4 562 190 A (UEDA IKUO ET AL) 31 December 1985 (1985-12-31) claims 1,6,7	1-100
A	US 4 797 399 A (UEDA IKUO ET AL) 10 January 1989 (1989-01-10) claims 1,5,6	1-100
A	US 4 859 700 A (LAVIELLE GILBERT ET AL) 22 August 1989 (1989-08-22) claims 1,7,8	1-100
A	US 5 132 305 A (BONNET JACQUELINE ET AL) 21 July 1992 (1992-07-21) claims 1,8-10	1-100

-/--

5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/21504

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SINGH ET AL: "Heterocyclic systems containing bridgehead nitrogen atom: Part XXV-syntheses of imidazo(2,1-b)benzothiazoles and quinoxalino(2,3:4',5')imidazo(2',1'-b)benz othiazoles" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC, INCL. MEDICINAL, PUBLICATIONS & INFORMATIONS DIRECTORATE, NEW DELHI, IN, vol. 14B, no. 12, 1976, pages 997-998, XP000953345 ISSN: 0019-5103 cited in the application table 1 ---	1,5
A	CHEMICAL ABSTRACTS, vol. 68, no. 1, 1 January 1968 (1968-01-01) Columbus, Ohio, US; abstract no. 2856m, page 269; XP002198025 cited in the application formula (V) & N SALDABOLS ET AL: "Synthesis in the methyl 2-furyl ketone series. XII. 5-Nitro-2-furyl substituted imidazo heterocyclic compounds with a common nitrogen atom" KHIM.-FARM. ZH., vol. 1, no. 2, 1967, pages 27-31, -----	96

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 2, 5-7, 11-13, 17-19, 23-25, 29 (part), 30, 31, 33, 35, 37, 39, 41-61 (part), 62, 63, 65, 67, 69, 71, 73-79 (part), 80, 81, 83, 85, 87, 89, 91-94 (part), 100 (part)

   Compounds of formula (I) of claim 1 wherein the alkyl substituent at Z has a keto group in beta-position, and the pharmaceutical use of these compounds.

2. Claims: 3, 4, 8-10, 14-16, 20-22, 26-28, 29 (part), 32, 34, 36, 38, 40, 41-61 (part), 64, 66, 68, 70, 72, 73-79 (part), 82, 84, 86, 88, 90, 91-94 (part), 95, 100 (part)

   Compounds of formula (II) of claim 3 wherein the alkyl substituent at Z has no keto group in beta-position, and the pharmaceutical use of these compounds.

3. Claim : 96

   Method of medical treatment making use of the tricyclic compound of formula (XIV)

4. Claims: 97-99

   Compounds of formula (XV) and their pharmaceutical use.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 29, 41-61, 73, 75-79, 91-93, 100

Present claims 29, 41-61, 73, 75-79, 91-93 and 100 relate to an extremely large number of possibilities. The methods of treatment claimed therein refer to any "tetrahydrobenzothiazole analogues". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds concerned: On page 20 of the description, the expression "tetrahydrobenzothiazole analogue" is defined as to comprise compounds falling actually within the formula (I) of claim 1 and the formula (II) of claim 3. Thus in the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds comprised by formula (I) of claim 1 and formula (II) of claim 3 and for methods making use of these compounds.

It is noted that all preparative examples and all pharmacological test examples refer to compounds which are in fact derivatives of tetrahydrobenzothiazoles; acoording to formulae (I) and (II), the claimed subject-matter also comprises the isosteric tetrahydrobenzoxazoles, tetrahydrobenzothiophenes and tetrahydrobenzofurans. All these possibilities have not been verified, however, they may be considered as to represent reasonable generalisations of the very experimental results put forward, and they have been searched as well.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/21504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0186087 A	02-07-1986	DE 3447075 A1	03-07-1986
		DE 3508947 A1	18-09-1986
		AT 45735 T	15-09-1989
		AU 583874 B2	11-05-1989
		AU 5154485 A	17-07-1986
		BG 62023 B2	30-12-1998
		BR 1100678 A3	13-10-1999
		CA 1263653 A1	05-12-1989
		CS 9104099 A3	16-09-1992
		DD 242230 A5	21-01-1987
		DE 3572485 D1	28-09-1989
		DK 590285 A	23-06-1986
		EP 0186087 A1	02-07-1986
		ES 550235 D0	16-01-1987
		ES 8702787 A1	01-04-1987
		ES 556873 D0	01-08-1987
		ES 8707513 A1	16-10-1987
		ES 556874 D0	01-08-1987
		ES 8707514 A1	16-10-1987
		ES 556875 D0	01-08-1987
		ES 8707515 A1	16-10-1987
		FI 855102 A ,B,	23-06-1986
		GR 853126 A1	22-04-1986
		HK 78692 A	23-10-1992
		HU 39736 A2	29-10-1986
		IE 58863 B	17-11-1993
		IL 77415 A	19-03-1990
		JP 1854941 C	07-07-1994
		JP 61155377 A	15-07-1986
		JP 5072907 B	13-10-1993
		KR 9309791 B1	11-10-1993
		LU 90208 A9	06-04-1998
		MX 9202792 A1	30-06-1992
		NO 855195 A ,B,	23-06-1986
		NZ 214661 A	26-04-1990
		PH 24533 A	03-08-1990
		PT 81735 A ,B	01-01-1986
		SG 82492 G	04-12-1992
		US 4843086 A	27-06-1989
		US 4886812 A	12-12-1989
		US 4731374 A	15-03-1988
		ZA 8509731 A	26-08-1987
DE 3923689 A	24-01-1991	DE 3923689 A1	24-01-1991
		AU 6149690 A	22-02-1991
		CA 2063988 A1	19-01-1991
		DD 298395 A5	20-02-1992
		WO 9101136 A1	07-02-1991
		EP 0483252 A1	06-05-1992
		HU 60922 A2	30-11-1992
US 3462448 A	19-08-1969	NONE	
DE 1926558 A	03-12-1970	DE 1926558 A1	03-12-1970
DE 4241013 A	09-06-1994	DE 4241013 A1	09-06-1994
		AT 183091 T	15-08-1999
		AU 674378 B2	19-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/21504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4241013 A		AU 5715294 A	04-07-1994
		BG 62475 B1	30-12-1999
		BG 99700 A	30-04-1996
		CA 2150131 A1	23-06-1994
		CN 1091635 A ,B	07-09-1994
		CZ 9501440 A3	13-03-1996
		DE 59309733 D1	16-09-1999
		DK 675717 T3	28-02-2000
		WO 9413287 A1	23-06-1994
		EP 0675717 A1	11-10-1995
		ES 2136725 T3	01-12-1999
		FI 952734 A	05-06-1995
		GR 3031521 T3	31-01-2000
		HK 1019003 A1	08-09-2000
		HU 71798 A2	28-02-1996
		IL 107870 A	05-12-1996
		JP 8504201 T	07-05-1996
		JP 3221880 B2	22-10-2001
		MX 9307644 A1	30-06-1994
		NO 952207 A	02-06-1995
		NZ 258876 A	27-07-1997
		PL 309282 A1	02-10-1995
		RU 2157685 C2	20-10-2000
		SG 49228 A1	18-05-1998
		SK 74095 A3	08-05-1996
		US 6191153 B1	20-02-2001
		ZA 9309065 A	04-08-1994
JP 10152488 A	09-06-1998	NONE	
JP 08113570 A	07-05-1996	NONE	
US 4769370 A	06-09-1988	NONE	
EP 0705832 A	10-04-1996	AU 698580 B2	05-11-1998
		AU 3049795 A	28-03-1996
		CA 2157998 A1	13-03-1996
		CN 1129219 A ,B	21-08-1996
		CZ 9502322 A3	13-03-1996
		EP 0705832 A1	10-04-1996
		FI 954243 A	13-03-1996
		HU 72593 A2	28-05-1996
		IL 115236 A	15-06-1998
		JP 8081464 A	26-03-1996
		NO 953575 A	13-03-1996
		NZ 272961 A	26-02-1998
		PL 310373 A1	18-03-1996
		RU 2146256 C1	10-03-2000
		TR 960794 A2	21-10-1996
		US 5563147 A	08-10-1996
		ZA 9507607 A	17-05-1996
EP 0281261 A	07-09-1988	AT 75723 T	15-05-1992
		AU 608293 B2	28-03-1991
		AU 1216788 A	01-09-1988
		CA 1338934 A1	25-02-1997
		DE 3870666 D1	11-06-1992
		DK 91488 A	27-08-1988

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/21504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0281261 A		EP 0281261 A2	07-09-1988
		ES 2037208 T3	16-06-1993
		FI 880906 A ,B,	27-08-1988
		GR 3004984 T3	28-04-1993
		IE 61257 B	19-10-1994
		IL 85342 A	14-01-1993
		JP 2677588 B2	17-11-1997
		JP 63264557 A	01-11-1988
		NO 880833 A ,B,	29-08-1988
		NZ 223440 A	26-02-1991
		PT 86836 A ,B	01-03-1988
		US 4847254 A	11-07-1989
		US 4946863 A	07-08-1990
		ZA 8801217 A	25-01-1989
US 4377695 A	22-03-1983	DE 3042481 A1	16-06-1982
		DK 495881 A	12-05-1982
		EP 0051827 A1	19-05-1982
		GR 74705 A1	05-07-1984
		JP 57108074 A	05-07-1982
		ZA 8107697 A	27-10-1982
US 4562190 A	31-12-1985	AT 37368 T	15-10-1988
		DE 3474145 D1	27-10-1988
		EP 0132817 A1	13-02-1985
		JP 1788070 C	10-09-1993
		JP 4081591 B	24-12-1992
		JP 60034964 A	22-02-1985
US 4797399 A	10-01-1989	AU 6762687 A	23-07-1987
		CN 87100707 A	02-09-1987
		DK 8687 A	18-07-1987
		EP 0232740 A1	19-08-1987
		FI 865369 A	18-07-1987
		JP 62181253 A	08-08-1987
		NO 870053 A	20-07-1987
		OA 8462 A	29-07-1988
		PT 84103 A	01-02-1987
		ZA 8609748 A	26-08-1987
US 4859700 A	22-08-1989	FR 2611713 A1	09-09-1988
		AT 63309 T	15-05-1991
		AU 598345 B2	21-06-1990
		AU 1234488 A	01-09-1988
		CA 1313871 A1	23-02-1993
		DE 3862660 D1	13-06-1991
		DK 104388 A	28-08-1988
		EP 0282390 A1	14-09-1988
		ES 2009553 A6	01-10-1989
		GR 88100111 A ,B	16-12-1988
		IE 60500 B	27-07-1994
		JP 1845506 C	25-05-1994
		JP 5058633 B	27-08-1993
		JP 63227582 A	21-09-1988
		NZ 223663 A	29-01-1990
		OA 8813 A	31-03-1989
		PT 86851 A ,B	01-03-1988
		US 4885299 A	05-12-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/21504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4859700 A		ZA 8801383 A	28-12-1988
US 5132305 A	21-07-1992	FR 2643634 A1	31-08-1990
		AU 626080 B2	23-07-1992
		AU 5019690 A	06-09-1990
		CA 2010989 A1	31-08-1990
		EP 0385848 A1	05-09-1990
		JP 2268172 A	01-11-1990
		JP 6002753 B	12-01-1994
		NZ 232701 A	29-01-1991
		OA 9439 A	15-10-1992
		PT 93278 A	31-08-1990
		US 5182278 A	26-01-1993
		ZA 9001543 A	30-01-1991